Guidelines for Aggressive Non Hodgkin's Lymphomas Vol IX

Part B

Editors

Dr. Brijesh Arora MD, DM
Associate Professor
Department of Medical Oncology

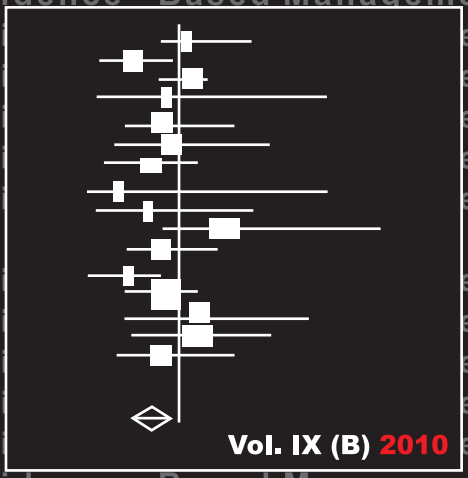
Dr. Manju Sengar MD, DM
Assistant Professor,
Department of Medical Oncology

Published by
Tata Memorial Hospital
Mumbai

Evidence Based Management of Cancers in India

(Two Parts)

Guidelines for Aggressive Non Hodgkin's Lymphoma (Part B)



Vol. IX (B) 2010

Tata Memorial Hospital

Guidelines for Aggressive Non Hodgkin's Lymphoma (Part B) Vol. IX (B) 2010

Tata Memorial Hospital
Dr. Ernest Borges Road, Parel
Mumbai 400 012. INDIA.
Tel.: +91-22-2417 7000 Fax: +91-22-2414 6937
Email: crs@tmc.gov.in
Website: http: //tmc.gov.in

Evidence Based Management of Cancers in India Guidelines

Two Parts

Set ISBN: 978-93-80251-01-1

Guidelines for Urological Cancers
Part A ISBN: 978-93-80251-02-8

Guidelines for Aggressive Non Hodgkin's Lymphomas
Part B ISBN: 978-93-80251-03-5

Set ISBN: 978-93-80251-01-1
Part B ISBN : 978-93-80251-03-5

Published by the Tata Memorial Hospital, Mumbai,
Printed at the Sundaram Art Printing Press, Mumbai.

Dedicated to
all our patients at
The Tata Memorial Hospital

Contents

Preface

The Centre for Evidence Based Medicine (EBM) defines EBM as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”. EBM has percolated into all fields and levels of medical practice and this has been particularly exemplified in current oncology practice. There is an increasing need to update our knowledge and be guided by EBM, especially in an era where there have been rapid developments and innovations in oncology.

Considerable progress has been made in diagnosis, response prediction, prognostication and management of Non Hodgkin’s lymphomas (NHL). The newer classification emphasizes the importance of clinical details, morphology, IHC and cytogenetics. Newer molecular techniques refine it further and help individualize treatment for patients. Treatment paradigms have changed considerably based on these new classification systems. After decades of no improvement in outcome, we have targeted therapy which has revolutionized the management of NHL with Rituximab now improving outcomes in both low grade and high grade lymphomas. Antibodies targeting CD

52 and CD 23 have also become established in treatment protocols and newer antibodies are being explored for specific lymphomas. New protocols are being investigated to manage relapsed and refractory lymphomas.

Information overload can be as much of a problem as paucity of information. The busy clinican is frequently unable to separate real data from sensational hype; the EBM meeting and guidelines book on aggressive NHLs is planned to do precisely this. As always, in addition to collating the best available evidence, the meeting and book also highlight areas where strong evidence is lacking. Exciting new research is ongoing in pediatric lymphoma, HIV and lymphoma, targeted therapy, vaccine therapy, DNA microarray and gene signatures for sub-classification of NHL and in many other areas. High grade lymphomas and pediatric lymphomas are not common malignancies; controversies in management can only be resolved with large multi centric studies. I hope that in addition to updating practicing oncologists, this book and meeting serves as a stimulus for investigators to actively participate in clinical research and further improve treatment outcomes.

February, 2010
Mumbai, India

R. A. Badwe
Director, Tata Memorial Centre

Diagnostic Algorithms for Aggressive B Cell Non Hodgkin's Lymphoma (NHL)

As per the WHO 2008 classification each lymphoma type is unique and identified based on its morphological, phenotypic, genotypic/cytogenetic, and clinical features. It is essential that pathologist talk the same language and diagnose entities listed in the WHO 2008 classification. This means that morphology based classification are not to be used in today's era.

Included under the broad term aggressive B cell lymphomas are" Precursor B lymphoblastic lymphoma, blastoid variants of mantle cell lymphoma, Burkitt lymphoma and the whole spectrum of Diffuse Large cell lymphoma(DLBL)and its variants. The first three would also qualify for the term "highly aggressive B cell lymphomas".

Plan of discussion

1. Prerequisites
2. Algorithm for diagnosis
3. Specific problematic zones in diagnosis

4. Current evidence for appropriately identifying subtypes of DLBL

1. Prerequisites

- Well fixed sections are an essential for appropriate interpretation
- Use of Ancillary techniques: - Immunohistochemistry is no longer an ancillary technique for lymphoma diagnosis it is essential and integral to lymphoma diagnosis. Molecular and cytogenetic evaluation should preferably be obtained in all cases but they are a must in problematic cases. Flow cytometry evaluation for confirmation of a mature B cell origin and evaluation of pattern of sIg expression often helps in some instances.

2. Algorithm for diagnosis

"Morphology forms the basis for any diagnostic algorithm"

Most of the aggressive B cell proliferations are diffuse. Slide eyeballing and morphology of individual cell type is a useful clue in ordering immunohistochemistry the chief adjuvant in the diagnostic algorithm given in chart 1. A large neoplastic B lymphoid cell typically has a nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte[1]. Unfortunately some diffuse large B cell lymphomas(DLBL's) do not fulfill this definition and thus pathologist have a tendency to include most unclassifiable B cell lymphomas that are not low grade into this category. A Burkitt's lymphoma shows intermediate sized cells with nuclear size similar to that of an endothelial cell nucleus or a macrophage nucleus with an amphophilic or basophilic cytoplasm and peripherally placed nucleoli.

Specific Problematic zones in diagnosis

I) *B cell lymphoma unclassifiable :* Though most clinicians prefer "one line diagnosis" and treatment based on clear protocols for defined diseases, there are lymphomas in the borderland category that transgress between two entities. This has reflected in the present WHO 2008 classification of NHL with creation of two categories

- *B cell lymphoma unclassifiable with features intermediate between DLBL and Burkitt lymphoma (BL):-*
  These are tumors that are morphologically like a Burkitt lymphoma but have atypical features like some cells smaller than those of typical DLBL, resembling BL, and some cells larger than those of typical BL, resembling DLBL but their immunophenotype is consistent with that of BL. It is essential to recognize BL accurately on histology as aggressive multiagent chemotherapy results in good response rate in patients. While BL in children are fairly homogenous those in adult are heterogeneous and carry only a 52% agreement amongst pathologist for diagnosis. Hence the creation of above category in WHO 2008 is justified but this category is not a wastebasket category and Table 1 documents the differentiating features.

  - Tumors with strong bcl-2 expression and a proliferation index below 95%. Less than 10% of typical BL that lack MYC rearrangement using FISH analysis, but these should not be included in this category.

- Dual or triple hit lymphomas – These are a group of B cell lymphomas that have a morphologic semblance to BL with a striking starry-sky pattern, but show greater nuclear polymorphism. While MYC rearrangement in mBL (molecular Burkitt as defined by a gene profiling signature) is IG-MYC type dual hit lymphomas have other partner genes (non IG-MYC). They have a "Myc-complex" pattern i. e:- non–*IG-myc* fusions or *IG-myc* fusions that have a high chromosomal complexity score, *IGH-BCL2* fusion, or *BCL6* breakpoint, or any combination of these and *MYC* translocations. Gene profiling studies have shown that patients with lymphomas classified as molecular BL(mBL) or myc-simple had a significantly better five-year survival rate than patients with non-mBL including myc-complex or myc-negative lymphomas. These results from gene profiling studies also mean that laboratories offering molecular cytogenetics should employ a full panel of MYC fusion probes (BCL2-IGH fusion probes, BCL6 break-apart probes, IGH break-apart probes, IGL break-apart probes) to clarify the distinction between Burkitt lymphoma(which is Myc simple) and diffuse large B cell lymphoma with MYC rearrangement(Myc complex).

To quote verbatim “The current imperfect modus operandi is to diagnose BL when the morphological appearance is acceptable (but not necessarily typical), the phenotype is typical and a MYC but not a BCL-2 or BCL-6 translocation is present”.

- ❑ Unclassifiable Blastic B cell lymphomas – There some blastic B cell lymphomas that have transformed from low grade lymphomas or undifferentiated mature B cell neoplasm’s that refuse categorization by traditional methods and continue to pose problems to both pathologists and clinicians for management [8].

- ➢ *B cell lymphoma unclassifiable with features intermediate between DLBL and Classical Hodgkin’s lymphoma*

  There are distinct variants of DLBL where the neoplastic B cell resemble Reed Sternberg cells of Hodgkin’s lymphoma (HL) and also have a reactive lymphoid background. Likewise syncitial variants of HL expressing CD20 mimic DLBL due to sheets Of B cells. The presence of uniform strong staining for pan B-cell markers such as CD20 and CD79a, positivity for B cell transcriptional factors such as Oct-2 and BOB.1, positivity for LCA/CD45 and lack of staining for CD15, although not specific, all support the diagnosis of DLBL over HL . However, there are a group of “gray zone” lymphomas, often within the mediastinum that fail such distinction and the above term is used

to depict such lesions. It is probably wise to err on the side of a NHL and to treat as such, but also to acknowledge the diagnostic difficulties and the importance of keeping an open mind in cases refractory to therapy. This topic will be covered more extensively in session on Gray zone lymphoma.

II) *CD20 negative aggressive B cell lymphomas:* With the inclusion of newer entities in WHO 2008 classification of B cell lymphomas, pathologists have to accept that there are subtypes of high grade B cell lymphoma that are CD20 negative yet B cell lymphomas. ALK positive diffuse large B cell lymphoma which is CD20 negative but expresses CD138 is a prototypical example of this group.

III) Plasmablastic lymphoma Vs myeloma

Both plasmablastic lymphomas and plasmablastic myelomas have overlapping morphologic patterns. This differential will be very important given diagrammatically opposite therapies for these tumors. There is a histological subtype of plasmablastic lymphoma - myeloma like which is the main culprit and the salient features for distinction between the two are summarized in table 2. But there is indeed no conclusive distinguishing feature for both these entities. In one study of 58 consecutive immunocompetent patients, plasmablastic cytomorphologic features were noted in 2 of 4 with plasmacytomas and 14 (26%) myelomas. Of these one plasmacytoma and three myelomas were EBER positive hence the dogma that EBER positive plasmablastic tumors are lymphomas has vanished. The most reliable features for distinction are:- presence of lytic bone lesions, M band or abnormal serum or urinary

protein. There are still no guidelines to accurately differentiate non secretory myelomas from plasmablastic lymphomas at an Immunohistochemical level.

IV) T cell rich B cell Vs nodular Lymphocyte predominant Hodgkins lymphoma:

Though the definition of T cell rich B cell lymphoma(TCRBCL) is presence of > 90% reactive inflammatory component and <10% neoplastic large B cells within this heterogeneous spectrum there are two subtypes. The first is the distinct TCRBCL as outlined in WHO 2008 as a tumor and second includes cases that transform from nodular lymphocyte predominant Hodgkins lymphoma (NLPHL). The consensus is that any tumor that has even a single nodule of expanded dendritic cell network with entrapped germinal large B cells should be labeled as nodular lymphocyte predominant Hodgkin's lymphoma with transformation and not as T cell rich B cell lymphoma. As synctial variant of nodular lymphocyte predominant Hodgkin's lymphoma is described there are no clear cut guidelines to document large B cell transformation in nodular lymphocyte predominant Hodgkin's lymphoma. However loss of dendritic cell network and presence of T cell rich areas indicate higher risk of disease dissemination. The outcomes of patients with NLPHL transformed to DLBCL indicate that their clinical course is more aggressive.

V) EBV positive diffuse large B cell lymphoma in elderly patients Vs Hodgkin's lymphoma:-

A close differential for EBER positive DLBL of elderly is EBER positive classical Hodgkin's lymphoma

(CHL). These HRS cells are all positive for CD30, and they are mostly positive for CD15 and negative for CD45. DLBCL of the elderly is usually positive for CD45, CD20/CD79a, variably positive for CD30 and negative for CD15. The RS cells in CHL express EBV type II latency with positive EBER, EBNA-1, LMP-1 and LMP-2A whereas the malignant cells of EBV + DLBCL of the elderly express type III latency. Thus, immunohistochemical studies for EBER latency are essential in the differential diagnosis of the above entities.

VI) Ki67 index in Aggressive lymphomas

As discussed early on Ki67 is useful in distinguisnhg Burkitt's lymphoma from DLBL. Only one study has demonstrated a cut-off value of 70% good and bad prognosis in DLBL when combined with other prognostic factors of low IPI score and bulky disease[17]. But conclusive evidence of use of Ki67 in prognostication of DLBL is lacking and the chief reason is that there are great technical variations in this stain. One study of Ki67 in mantle cell lymphoma documented that the Ki-67 index estimated by eyeballing by 11 experienced hematopathologists deviated considerably between individual observers (deviation up to 85%) [18].

3. Current evidence for appropriately identifying subtypes of DLBL

DLBL is a heterogeneous entity that includes a number of different variants and subtypes and a spate of studies addressed the issue of identifying prognostically meaningful subsets within this category. The current paradigm is that DLBL of germinal centre (GC) type, as defined by gene profiling studies have better prognosis than other DLBL.

Since gene-expression profiling is not generally available for diagnostic purposes in daily practice, “translations” to immunohistochemical algorithms have been defined. This immunophenotypic translation correlates with the gene-expression profiling in around 70- 80% of the cases. An agreed on algorithm for classifying DLBL is lacking and results for their reproducibility and the prognostic impact are conflicting. The chief amongst these algorithms have been summarized in diagram 1. The results of Immunohistochemical class prediction and prognostic stratification of diffuse large B-cell lymphoma (DLBCL) have been marred by biologic variation in type of therapy used in most studies, variations occur due to differences in laboratory techniques, scoring definitions, and inter- and intra observer variations. The Lunenburg group encompassing nine leading clinical lymphoma research groups from Europe, United States, and Canada however also showed that when optimal-quality staining is used, the overall reproducibility and the agreement on classification as ABC- versus GCB-like DLBCL using Immunophenotyping improved significantly when strict scoring guidelines were used. To conclude the immunohistochemical and molecular subgroups of DLBCL NOS are only considered as variants with a similar level of relative (or un) importance as morphologic variants and are not designated as separate entities.

In contrast to immunophenotypic subtypes in DLBL-NOS, clinicopathological entities like primary DLBCL of CNS, primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, and intravascular large B-cell lymphoma should definitely be identified and diagnosed. Although molecular studies have shown that DLBCL associated with chronic inflammation and nodal diffuse large B-cell lymphoma have significant different gene expression

profiles, EBV-positive diffuse large B-cell lymphoma of the elderly and DLBCL associated with chronic inflammation have no single morphological or phenotypical feature that distinguish them from DLBCL not otherwise specified (NOS). Therefore, the clinicopathological correlation is the gold standard in the diagnosis of these entities[2]. Viral markers are now advocated in diagnosis of some specific entities like HHV8 and EBV associated B cell lymphoma, EBV-positive diffuse large B-cell lymphoma of the elderly, DLBCL associated with chronic inflammation and large B-cell lymphoma arising in HHV-8- associated multicentric Castleman disease). All the aforementioned entities are characterized by a very aggressive behavior and short survival regardless of stage at diagnosis.

References

1. Prakash S, Swerdlow SH. Nodal aggressive B-cell lymphomas: a diagnostic approach. J Clin Pathol. 2007;60:1076-85.
2. Balague Ponz O, Ott G, Hasserjian RP, Elenitoba-Johnson KS, de Leval L, de Jong D. Commentary on the WHO classification of tumors of lymphoid tissues (2008): aggressive B-cell lymphomas. J Hematop. 2009; 2: 83–87.
3. Hasserjian RP, Ott G, Elenitoba-Johnson KS, Balague-Ponz O, de Jong D, de Leval L. Commentary on the WHO classification of tumors of lymphoid tissues (2008): “Gray zone” lymphomas overlapping with Burkitt lymphoma or classical Hodgkin lymphoma. J Hematop. 2009; 2: 89–95.
4. McClure RF, Remstein ED, Macon WR, Dewald GW, Habermann TM, Hoering A, Kurtin PJ. Adult B-cell lymphomas with burkitt-like morphology are

phenotypically and genotypically heterogeneous with aggressive clinical behaviour. Am J Surg Pathol 2005;29:1652–1660.

5. Haralambieva E, Boerma EJ, van Imhoff GW, Rosati S, Schuuring E, Müller-Hermelink HK, Kluin PM, Ott G. Clinical, immunophenotypic, and genetic analysis of adult lymphomas with morphologic features of Burkitt lymphoma. Am J Surg Pathol. 2005;29:1086-94.
6. Dave SS, Fu K, Wright GW, Lam LT, Kluin P, Boerma EJ, Staudt LM et al and Lymphoma/ Leukemia Molecular Profiling Project. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med. 2006;354:2431-42.
7. Bellan C, Stefano L, Giulia de F, Rogena EA, Lorenzo L. Burkitt lymphoma versus diffuse large B-cell lymphoma: a practical approach. Hematol Oncol. 2009;27:182-5.
8. de Jong D. Novel lymphoid neoplasms—the borderland between diffuse large B-cell lymphoma and Burkitt's lymphoma. Haematologica. 2009;94:894-6.
9. Choi WW, Weisenburger DD, Greiner TC, Piris MA, Banham AH, Delabie J, et al. .A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res. 2009;15:5494-502.
10. de Jong D, Rosenwald A, Chhanabhai M, Gaulard P, Klapper W, Lee A, Sander B, Thorns C, Campo E, Molina T, Norton A, Hagenbeek A, Horning S, Lister A, Raemaekers J, Gascoyne RD, Salles G, Weller E; Lunenburg Lymphoma Biomarker Consortium. Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation

of tissue microarray as a prerequisite for broad clinical applications—a study from the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol. 2007;25:805-12.

1. **Nodal aggressive B-cell lymphomas: a diagnostic approach.**

   Prakash S, Swerdlow SH.

   J Clin Pathol. 2007 Oct;60(10):1076-85.

The diffuse aggressive B-cell lymphomas, as recognised in the 2001 WHO classification, represent a clinically and biologically heterogeneous group of neoplasms that require very different therapeutic approaches and have very different outcomes. They should be diagnosed using a multiparameter approach that emphasises morphological and immunophenotypic studies, and in at least some cases, relies on cytogenetic and/or genotypic studies. Incorporation of clinical data may be important as well. There is also current interest in going beyond the basic diagnosis and providing pathological prognostic information when possible. Whereas the diagnosis of some cases will be relatively easy, the differential diagnosis in others is very difficult, with some cases in a grey zone between two different well defined categories.

2. **Adult B-cell lymphomas with burkitt-like morphology are phenotypically and genotypically heterogeneous with aggressive clinical behavior.**

   McClure RF, Remstein ED, Macon WR, et al.

   Am J Surg Pathol. 2005 Dec;29(12): 1652-60

Adult, de novo B-cell lymphomas meeting the WHO morphologic criteria for atypical Burkitt/Burkitt-like lymphoma cause diagnostic difficulty for pathologists because the genetic and clinical characteristics of this group of lymphomas have not been clearly defined. Thirty-one such lymphomas, designated as Burkitt-like lymphomas (BLL), were selected based on morphologic features and evaluated for immunophenotype, MYC and BCL2 status, and clinical features. Nine childhood Burkitt lymphomas (BL) and 87 adult, de novo diffuse large B-cell lymphomas (DLBL) were similarly evaluated for comparison. The BL group demonstrated uniform characteristics: all had Burkitt lymphoma morphology, an identical immunophenotype (positive for CD20, CD10, bcl-6, CD43, and p53; negative for CD138, CD23, bcl-2), high MIB-1 positivity, IGH/MYC translocation, no IGH/BCL2 translocation, and all patients were alive at the last follow-up. The BLL and DLBL groups were heterogeneous. Burkitt-like morphology alone correlated with decreased survival. IGH/MYC or IGL/MYC fusion was identified in 11 of 27 (41%) BLL and 4 of 76 (5%) DLBL and was associated with decreased survival in both groups. MIB-1 positivity did not correlate with morphology, MYC abnormalities, or survival. We propose that adult B-cell lymphomas with BLL morphology are a phenotypically and genetically heterogeneous group of aggressive lymphomas, biologically distinct from childhood BL. Until biologically accurate subgroups within this morphologically defined group are identified, it is appears that both recognition of BLL morphology and direct evaluation for the presence of MYC fusion to immunoglobulin genes are important for identification of adult patients with poorer prognosis than those with DLBL.

3. Burkitt lymphoma versus diffuse large B-cell lymphoma: a practical approach.

Bellan C, Stefano L, Giulia de F, et al.

Hematol Oncol. 2009 Dec;27(4):182-5.

Burkitt Lymphoma (BL) is listed in the World Health Organization (WHO) classification of lymphoid tumours as an "aggressive B-cell non-Hodgkin's lymphoma", characterized by a high degree of proliferation of the malignant cells and deregulation of the c-MYC gene. The main diagnostic challenge in BL is to distinguish it from diffuse large B-cell lymphoma (DLBCL). While in children BL and DLBCL types probably do not differ clinically, and the differential diagnosis between BL and DLBCL may theoretically appear clear-cut, in adults daily practice shows the existence of cases that have morphological features, immunophenotypic and cytogenetics intermediate between DLBCL and BL, and cannot be classified with certainty in these categories. Distinguishing between BL and DLBCL is critical, as the two diseases require different management. This review summarizes the current practical approach, including the use of a large panel of antibodies, and cytogenetic and molecular diagnostic techniques, to distinguish between BL, DLBCL and the provisional category of "B-cell lymphoma, unclassificable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma", now listed in the updated WHO classification.

4. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy.

Choi WW, Weisenburger DD, Greiner TC, et al.

Clin Cancer Res. 2009 Sep 1;15(17):5494-502.

PURPOSE: Hans and coworkers previously developed an immunohistochemical algorithm with approximately 80% concordance with the gene expression profiling (GEP) classification of diffuse large B-cell lymphoma (DLBCL) into the germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes. Since then, new antibodies specific to germinal center B-cells have been developed, which might improve the performance of an immunostain algorithm.

EXPERIMENTAL DESIGN: We studied 84 cases of cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP)-treated DLBCL (47 GCB, 37 ABC) with GCET1, CD10, BCL6, MUM1, FOXP1, BCL2, MTA3, and cyclin D2 immunostains, and compared different combinations of the immunostaining results with the GEP classification. A perturbation analysis was also applied to eliminate the possible effects of interobserver or intraobserver variations. A separate set of 63 DLBCL cases treated with rituximab plus CHOP (37 GCB, 26 ABC) was used to validate the new algorithm.

RESULTS: A new algorithm using GCET1, CD10, BCL6, MUM1, and FOXP1 was derived that closely approximated the GEP classification with 93% concordance. Perturbation analysis indicated that the algorithm was robust within the range of observer variance. The new algorithm predicted 3-year overall survival of the validation set [GCB (87%) versus ABC (44%); $P < 0.001$], simulating the predictive power of the GEP classification. For a group of seven primary mediastinal large B-cell lymphoma, the new algorithm is a better prognostic classifier (all “GCB”) than the Hans’ algorithm (two GCB, five non-GCB).

CONCLUSION: Our new algorithm is significantly more accurate than the Hans’ algorithm and will facilitate risk stratification of DLBCL patients and future DLBCL research using archival materials.

Table 1: Approach to Resolve Differential between Burkitt's Lymphoma and Diffuse Large B cell lymphoma [9,10]

	DLBL	B cell lymphoma unclassifiable with features intermediate between DLBCL and BL	Burkitt lymphoma
Morphology	Variable, ranging from medium-sized to BL-like morphology wit or without nucleoli pleomorphic nuclei	large, with a large cells medium-sized, round	Cohesive, starry-sky, medium sized cells, round nuclei with multiple nucleoli
Immunophenotype	CD10/bcl2/bcl6/ MUM1 variable, Ki67 <90%	CD10+/bcl2 strong/ bcl6+/MUM1 variable Ki67 : 5->95%	CD10+/Bcl6+/Bcl2-/ / MUM1 variable Ki67 >90%

(Contd...)

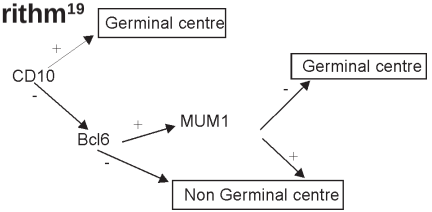
(Contd...)

	DLBL	B cell lymphoma unclassifiable with features intermediate between DLBCL and BL	Burkitt lymphoma
Epstein Barr Virus analysis	EBER+, LMP1, LMP2 and EBNA2 +.		EBER+, occasionally EBNA1+, LMP1-/ EBNA2-
Molecular cytogenetics	MYC:5-15% Bcl2: 30% Bcl6: 30%	MYC:80% bcl2 translocation-35 – 50 % bcl6 translocation – 5% Double hit lymphomas	MYC: 90 to 100%, bcl2 and bcl6 translocation absent
	MYC complex *		MYC simple
*dual hit lymphomas – as discussed in text			

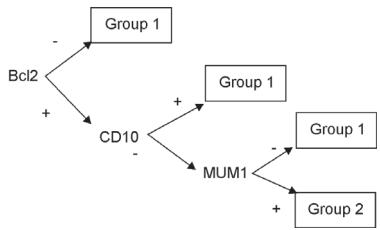
Table 2: Plasmablastic myeloma Vs Plasmablastic lymphoma		
	Plasmablastic Myeloma / plasmacytoma	**Plasmablastic Lymphoma**
Clinical features	Lytic bone lesions, M band or serum or urinary protein demonstration	Extranodal presentation No evidence of serum protein secretion and absence of osteolytic bone lesions
Morphology	Mature plasma cells admixed with Nucleolated blasts	Nucleolated blasts are the predominant population of cells
EBER	Usually negative (exceptions exist) AJCP	Usually positive
MIB1	Variable	90-100%
Cyclin D1	Positive	Negative
CD56	Positive	Negative

Diagram 1:
Algorithms suggested for Immunohistochemical Translation of Gene Profiling Studies in DLBL

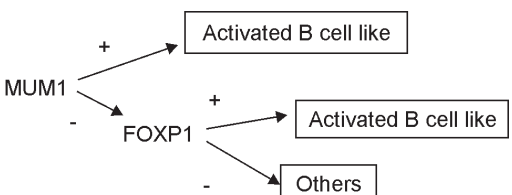
I) Hans algorithm[19]



II) Muris algorithm[20]



III) Modified activated B cell Algorithm [21]



IV) Algorithm proposed in September

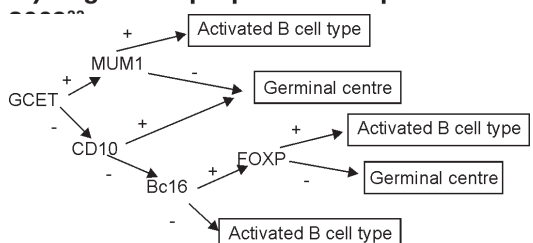
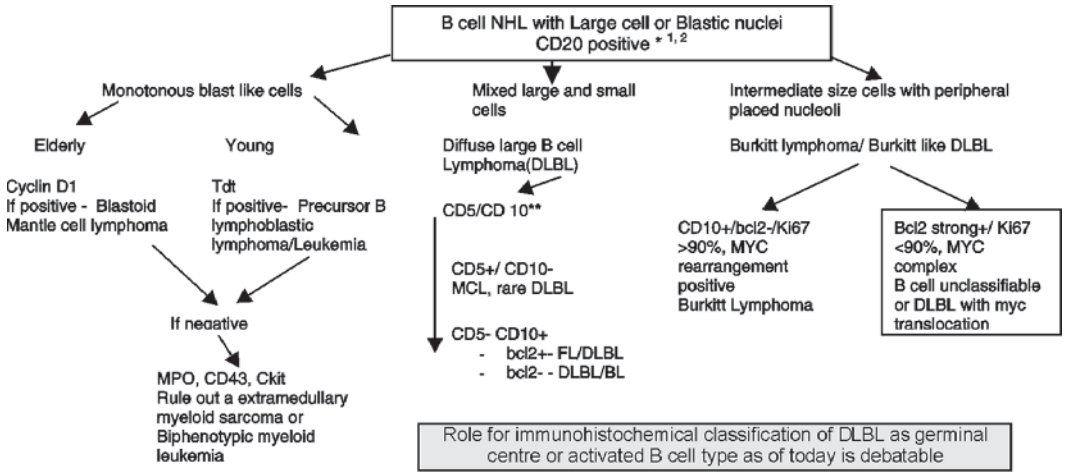


Chart 1: Algorithm for Aggressive B cell Lymphomas



Abbreviations- MCL – mantle cell lymphoma, FL- Follicular lymphoma,
*CD20 negative B cell lymphomas exist and are recognized using other pan-B cell antibodies Viz:- CD79a, PAX-5 or CD19, Some of these show post germinal centre differentiation and label with plasma-cell associated antigens such as CD138 or cytoplasmic immunoglobulin
**Required to differentiate unusual mantle cell or follicular lymphomas

Diagnostic Algorithms in Tissue-based T-cell Lymphomas

This review focuses on diagnostic algorithms in tissue based T-cell rich lesions. The discussion will be grouped into following categories: a) bone marrow (BM) based diseases, b) lymph node (LN) based proliferations c) cutaneous proliferations d) gastrointestinal infiltrates e) mediastinal lesions.

Diagnostic algorithms in BM based T-cell proliferations: Most of the BM based T-cell neoplasms, also involve peripheral blood (PB). Hence, in a greater proportion of cases, the diagnosis is made on PB film and flow cytometry. However, in a proportion of cases BM trephine biopsy (BMTB) is performed, either because the PB investigation is inconclusive or patient presents with low white cell counts.

Morphological clues in BMTB:

1) Presence of a monomorphic interstitial or diffuse infiltrate with cells having fine chromatin and inconspicuous nucleoli should raise the suspicion of T-lymphoblastic leukaemia/lymphoma (T-ALL/LBL).

2) Presence of a heavy diffuse infiltrate (diffuse packed marrow) of small to medium sized atypical lymphoid cells with coarse chromatin is often associated with T-cell prolymphocytic leukaemia (T-PLL). T-PLL cells often have a recognizable nucleolus

3) Interstitial small T-cell infiltrate that may also accompanied by excess B-cells and presence of B-cell nodules is typical of T-cell large granular lymphocytic leukaemia (T-LGL). T-cells usually account for <50% of the marrow cells.

4) Presence of intravascular significantly atypical intermediate sized T-lymphoid cells (rarely large cells) is characteristic of hepatosplenic T-cell lymphoma (HTL).

5) Intermediate or large sized lymphoid cells with multilobated nuclei patchily involving the marrow should raise the possibility of adult T-cell leukaemia lymphoma (ATLL). Increased osteoclastic activity and bone destruction is frequent.

6) Presence of a polymorphic infiltrate which in addition to T-cells includes large atypical cells and histiocytes should raise the suspicion of BM involvement by a nodal T-cell lymphoma, classic Hodgkin lymphoma (cHL), T-cell/histiocyte rich B-cell lymphoma (THRBCL) or haemophagocytic syndrome.

Immunophenotyping/immunohistochemistry: The choice of performing flow cytometry on BM aspirate specimens or performing immunohistochemistry on BMTB sections is more often dependent on local practices and policies. Both methods have their individual advantages and the information is complementary.

Diffuse packed marrow by CD3 positive cells:

1) Cells are small to intermediate in size and have fine chromatin – immunohistochemistry to include TdT, CD99, CD1a, CD4, CD8, CD2, CD5, CD7, CD10, CD79a, PAX5, CD34, myeloperoxidase and CD117. Expression of TdT defines a precursor cell lesion. Based in antigen expression T-ALL/LBL can be subtyped as: pro-T (cCD3+, CD7+, CD2-, CD1a-, CD34+/-, CD4- & CD8-); pre-T (cCD3+, CD7+, CD2+, CD1a-, CD34+/-, CD4- & CD8-); cortical T (cCD3+, CD7+, CD2+, CD1a+, CD34-, CD4+ & CD8+); and medullary T (sCD3+, cCD3+, CD7+, CD2+, CD1a-, CD34-, and expressing CD4 or CD8). Rare cases with absence of TdT and positivity to CD99 or CD1a are encountered. Co-expression of B-cell markers or myeloid markers would raise the possibility of acute leukaemias with aberrant antigen expression or 'biphenotypic' leukaemias. In the absence of TdT or CD1a, T-PLL or ATLL should be considered (see below).

2) Cells are small to intermediate in size and have coarse chromatin - immunohistochemistry to include TdT, CD4, CD8, CD2, CD5, CD7, CD25 and FOXP3. If TdT is positive follow alternate algorithm (above). CD8 is negative in over 60% of T-PLL and most of ATLL. Positivity for CD4, and typically absence of CD25 and FOXP3 expression is noted in T-PLL. On the other hand, ATLL cells express CD4, CD25 and FOXP3. Immunohistochemistry with TCL1 and cytogenetics (inversion of chromosome 14, t(14;14) with breakpoints on q11 and q32 or t(X;14(q28;q11)) would be helpful. A diagnosis of ATLL should be supported by a positive HTLV-1 serology. T-PLL and

ATLL can present with patchy infiltrates in the marrow.

Excess of interstitially located CD3 positive cells of small to intermediate in size with coarse chromatin: Immunohistochemistry to include TdT, CD4, CD8, CD2, CD5, CD7, CD16, CD56, CD57 and cytotoxic molecules (TIA1, perforin and granzyme B). If CD4 or TdT are positive, use alternate algorithms.

1) Expression of CD8, CD16 and CD57 along with cytotoxic molecules with variable loss of pan-T-cell antigens is typical of T-LGL. In T-LGL, there is often a considerable small B-cell infiltrate including presence of B-cell aggregates. Less than one-third of T-LGL is CD4&CD8 negative and would raise a differential diagnosis with HTL.

2) Expression of CD56 along with cytotoxic molecules, and with absence of CD4 and CD8 expression would raise the possibility of aggressive NK cell leukaemia. Most of these are also CD16 positive. Chronic lymphoproliferative disorders of NK cells have a similar immunophenotype with the exception of uniform expression of CD8.

Intravascular localization CD3 positive atypical cells of intermediate to large size: Immunohistochemistry to include TdT, CD4, CD8, CD2, CD5, CD7, CD56, CD57 and cytotoxic molecules. If CD4 or TdT are positive, use alternate algorithms. Lack of expression of both CD4 and CD8 along with expression of cytotoxic molecules is typical of HTL. In addition, there is variable expression of CD56 and variable loss of pan-T-cell antigens. A small proportion of cases are CD8 positive. Absence of TCR-beta can be confirmed by immunostaining (beta F1 antibody). While most cases are of gamma/delta

phenotype, a lesser proportion is of alpha/beta phenotype.

Polymorphous infiltrate with excess of CD3 positive cells in addition to histiocytic cells: Work-up to include CD4, CD8, CD2, CD5, CD7, CD56, CD57, cytotoxic molecules, CD10, CD21, PD-1, CD68R, CD15, CD30 and EBER (ISH).

1) Presence of atypical cells of variable size including larger and nucleolated cells positive for CD3 and CD4 should raise the possibility of peripheral T-cell lymphomas, especially angioimmunoblastic T-cell lymphoma (AIL). Approach should be similar to LN based diseases.

2) BM involvement by cHL or THRBCL also needs to be considered (discussed later).

3) If the T-cell infiltrate is not clearly atypical and is admixed with plasma cells, the possibility of a reactive/inflammatory/infective process should be considered. The T-cells are an admixture of CD4 and CD8 positive cells. Some of these cases, where the atypia is equivocal, T-cell clonality studies with T-cell receptor gene rearrangement studies may be indicated.

Prominent histiocytic infiltrate admixed with CD3 positive cells of variable density: Work-up to include CD4, CD8, CD2, CD5, CD7, CD56, CD57, cytotoxic molecules, CD10, CD21, PD-1, CD68R, CD163, CD15, CD30, HHV8-LANA1 and EBER.

1) Both H&E and CD68R should be carefully evaluated for number of histiocytes and for presence of haemophagocytosis. Once haemopathocytosis is

documented, an underlying lymphoma should be excluded. Possible viral association with EBV or HHV8 are also to be documented.

2) Histochemical stains for infective aetiology should be undertaken.

Diagnostic algorithms in LN based CD3 positive T-cell proliferations: The entities to be considered are: a) T-ALL/LBL b) Peripheral T-cell lymphoma, not otherwise specified (PTCLu) c) Angioimmunoblastic T-cell lymphoma (AIL) d) Anaplastic large cell lymphoma (ALCL) e) ATLL f) LN involvement by cutaneous T-cell lymphomas, especially mycosis fungoides (MF) h) infective/reactive proliferations.

Morphological clues:

1) Presence of a monomorphic diffuse infiltrate of small to intermediate sized cells with fine chromatin and inconspicuous nucleoli should raise the suspicion of T-ALL/LBL.

2) Cohesive tumour cells seen in a prominent sinusoidal pattern or in perivascular localization should raise suspicion of ALCL. ALCL cells can have extremely variable cytological features and can be variably accompanied by other non-neoplastic cells including histocytes, granulocytes and reactive lymphoid cells.

3) Presence of a diffuse polymorphous pattern with or without remnant/hyperplastic/burnt-out follicles, and presence of a large number of vessels with features of high endothelial venules should raise suspicion of PTCLu or AIL. Typically, the neoplastic cells of AIL have pale staining / clear cytoplasm.

4) ATLL involving the LN shows a diffuse pattern. However, the cells have extremely variable cytological features. A high degree of suspicion is essential.

5) In patients of MF, LNs with early involvement by MF typically show patchy areas of involvement. The background uninvolved LN shows features of dermatopathic lymphadenopathy.

6) Reactive T-zone expansions including viral infections and drug reactions can mimic PTCLu and AIL.

Diffuse monomorphic infiltrates of intermediate sized CD3 positive lymphoid cells with fine chromatin: Work-up should include TdT, CD1a, CD99, CD2, CD5, CD7, CD4, CD8 and Ki-67. Approach is similar to that of BMTB.

Large cell lymphomas expressing CD3: Work-up should include CD2, CD5, CD7, CD43, CD4, CD8, CD30, CD15, ALK, cytotoxic molecules, PAX5, EMA, EBER and Ki-67. Expression of CD30 in most of the neoplastic cells raises the possibility of ALCL. There is variable loss of T-cell antigens (including CD3 in some cases) and aberrant expression of EMA. They are more frequently CD4 positive and show aberrant expression of cytotoxic molecules. ALK expression defines ALCL, ALK positive type. Cases that qualify for the diagnosis of ALCL, which are ALK negative are currently classified as ALCL, ALK negative type. It is important to exclude cHL in cases that are ALK negative by evaluating PAX5 and EBER stains. While ALCL is consistently PAX5 negative, most cHL show weak expression of PAX5. Exceptional cases of ALCL express CD15, though CD15 expression is more indicative of cHL. It should also be noted that cHL can show aberrant expression of T-cell markers. Hence,

PAX5 immunostaining is critical. It should be noted that many other lymphomas including other T-cell lymphomas can be CD30 positive.

If CD30 is not uniformly positive in all cells, other T-cell lymphomas like PTCLu, AIL and ATLL should be considered.

Polymorphous infiltrates rich in atypical T-cells: Work-up should include CD2, CD5, CD7, CD4, CD8, PD-1, CD10, BCL6, CD21, CD30, CD15, ALK, cytotoxic molecules, light chains, EBER (ISH) and Ki-67. The main contenders in this category are PTCLu, AIL and reactive T-zone expansions. Rare cases of ATLL, ALCL or secondary involvement by an extranodal T-cell lymphoma need to be excluded in some cases. Both PTCLu and AIL are predominantly CD4 positive lymphomas, which may also show loss of some of the pan-T-cell antigens. Following features favour a diagnosis of AIL over PTCLu – expression of PD-1, CD10, BCL6 or CXCL13; presence of CD21 positive FDC meshworks around high endothelial venules outside the limits of the follicles; and presence of large EBV-positive B-cells which could either be polytypic or monotypic. Florid and atypical T-zone reactions are difficult to exclude based only on immunohistochemistry. Correlation with histological features and TCR gene rearrangements studies may be essential.

Two other entities that need to be considered are THRBCL and cHL. The T-cells in these two entities are benign, and the neoplastic component is the large B-cell component. The T-cells of THRBCL unlike those of AIL or PTCLu are mostly of CD8 type. However, the T-cells in cHL are of CD4 type similar to PTCLu and AIL. It should be noted that rarely AIL can have large atypical cells with all features of cHL.

Diagnostic algorithms in cutaneous CD3 positive T-cell infiltrates: Clinical information is critical in the evaluation of cutaneous T-cell lesions. The more common T-cell lymphomas of skin include MF, Sezary syndrome (SS) and cutaneous CD30-posiitve T-cell lymphoproliferative disorders (lymphomatoid papulosis (LyP) and cutaneous anaplastic large cell lymphoma (cALCL)). Less common entities are subcutaneous panniculitis like T-cell lymphoma (SPTL), primary cutaneous gamma delta T-cell lymphoma (PCGDTL), primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma (PCAECTL), primary cutaneous CD4 positive small/medium T-cell lymphoma, ATLL, AIL and NK/T-cell lymphoma.

Morphological clues:

1) Morphology of MF varies with the disease phase – patch, plaque and tumour phases of disease. Epidermotropism is a constant feature.

2) Morphology of LyP varies with the type, and its most typical morphology is seen in type A. LyP, type B can be confused with MF without adequate clinical information. Similarly, LyP, type C has morphological and biological continuum with cALCL, and clinical features apart from morphology are critical in making the distinction. In cALCL, >50% of the lesional cells are neoplastic CD30 positive T-cells.

3) SPTL needs to be differentiated from lupus panniculitis (LP) and PCGDTL. SPTL typically spares the septae separating the fat lobules unlike LP. Atypical T-cells admixed with histiocytes rim the adipocytes in SPTL. Other histological clues for diagnosis of LEP include dermal and subcutaneous mucin deposition, plasma cell infiltrates and

germinal centre formation. SPTL in contrast to PCGDTL spares the dermis (relatively) and the epidermis.

Small or intermediate sized T-cell infiltrates involving dermis and epidermis (epidermotropism/epidermal ulceration): Entities with this morphology more likely include MF, LyP-type B, PCGDTL and PCAECTL. Immunostains should include CD2, CD5, CD4, CD8, CD30, cytotoxic molecules, CD56 and Ki-67. Most cases of MF and LyP-type B are of CD4 type. Typically PCGDTL is negative for both CD4 and CD8, and PCAECTL is of CD8 type. A proportion of PCGDTL are positive for CD56. Both PCAECTL and PCGDTL lack CD5, express cytotoxic proteins, and have a high Ki-67 expression. LyP-type B usually has low Ki-67 expression and the proliferation is MF is variable (with the disease phase). Distinction between LyP-type B and MF may need clinical inputs. Early lesions of MF can be difficult to distinguish from inflammatory dermatoses with intense T-cell infiltrates. Apart from the morphological features, the CD4:CD8 ratio of the infiltrate can be a useful guide. A CD4:CD8 ratio of >10 (discounting for CD4 positive histiocytes) is highly indicative of MF and >5 would be suspicious of MF. In many of such cases, additional support through establishing T-cell clonality by PCR analysis for TCR gene rearrangement would be critical.

Nodular dermal infiltrates of large cells with or without epidermal involvement: Entities with this morphology more likely include tumour phase of MF, LyP-type A, LyP-type C, and cutaneous ALCL. Immunostains should include CD2, CD5, CD4, CD8, CD30, ALK, EMA, cytotoxic molecules, CD56 and Ki-67. Most of these lymphomas are of CD4 type, and the neoplastic cells in LyP-type A, LyP-type C, and cutaneous ALCL consistently

express CD30. Distinguishing these three is partly dependent on the evaluating the ratio of neoplastic to non-neoplastic cells in the lesion. It is least in LyP-type A, and it exceeds 1:1 in cALCL. cALCL, unlike ALCL (systemic ALCL involving skin) is negative for ALK, and often negative for EMA. In all cases of cALCL and LyP-type C, ALK expression should be evaluated, as systemic ALCL has a completely different biology. Furthermore, a proportion of tumour cells may express CD30 in tumour phase of MF.

Polymorphous dermal infiltrates with or without large cells: Entities with this morphology more likely include LyP-types A/C, primary cutaneous CD4 positive small/medium T-cell lymphoma, AIL, primary cutaneous THRBCL and reactive lymphoid proliferations. Work-up should include CD2, CD5, CD7, CD4, CD8, PD-1, CD10, CD21, CD30, CD15, ALK, cytotoxic molecules, light chains, EBER and Ki-67. LyP and cALCL are approached similar to earlier discussion. Primary cutaneous CD4 positive small/medium T-cell lymphoma has features similar to nodal PTCLu.

Panniculitis pattern of T-cell infiltrate: Entities with this morphology include SPTL, PCGDTL and LEP. Work-up should include CD2, CD5, CD4, CD8, CD30, cytotoxic molecules, CD56, EBER and Ki-67. The lymphoid cells in SPTL express CD8 and cytotoxic molecules, with variable loss of pan-T-cell antigens. They are also positive for TCR-beta and negative for CD4 and EBER. Distinction of SPTL from LEP is based on morphological features, an appropriate clinical setting and prominence of CD4 positive T-cell infiltrates, and if necessary T-cell receptor gene rearrangement studies. Typically, the lymphoid cells in PCGDTL are negative for both CD4 and CD8, and they express cytotoxic molecules. In

addition, there is variable expression of CD56 and variable loss of pan-T-cell antigens. A small proportion of cases are CD8 positive. PCGDTL is typically negative for TCR-beta expression. Rare cases of NK/T-cell lymphoma involving skin can have a panniculitis-like pattern. They more commonly present in nasal cavity and paranasal sinuses. These cells are positive for CD56, cytotoxic molecules and EBER, and negative for CD5, CD4 and CD8. NK/T-cell lymphomas do not have clonal TCR gene rearrangements.

Diagnostic algorithms in CD3 positive T-cell rich intestinal lesions: These include small intestinal biopsies, or resections specimens of the small intestine following a perforation. The likely diagnoses to be considered include enteropathy-associated T-cell lymphoma (EATL) - type A, EATL - type B, celiac disease (CD), resistant celiac disease (RCD), NK/T-cell lymphoma and inflammatory/ reactive lesions.

Work-up for biopsy specimens suspected to be CD or RCD should include CD4, CD8 and CD56. Apart from the morphological features of CD, it is important to confirm the phenotype of the intraepithelial lymphocytes (positive for CD3 and CD8, and negative for CD56) and to count them (numbers/100 surface enterocytes). The numbers exceed 30. In RCD, there is loss of CD8. Furthermore, in some cases of RCD, T-cell clonality studies using TCR gene rearrangements would be indicated to exclude early progression to EATL.

In cases suspected to be EATL- type A or type B and NK/T-cell lymphoma, work-up should include CD2, CD5, CD5, CD56, CD4, CD8, CD30, ALK, EMA, cytotoxic molecules, EBER and Ki-67. ETL-type A has extremely variable morphology. Furthermore the adjoining mucosa shows features of CD. On the other hand EATL-type B

has a more monomorphic infiltrate. EATL-type A is CD4 negative and expresses cytotoxic molecules with variable expression of CD8 and loss of some of the pan-T-cell antigens, where as type B expresses CD56 in addition to CD8. EATL is negative for EBV in contrast to NK/T-cell lymphoma, which is consistently associated with EBV. Furthermore, NK-T-cell lymphomas are negative for CD8. There is variable CD30 expression in all these lymphomas. Hence, establishing lack of ALK expression is essential to exclude rare cases of ALCL presenting in the gut.

A variety of reactive/inflammatory conditions may show prominent T-cell infiltrates. They are often accompanied by other reactive populations – B-cells, plasma cells, histiocytes and eosinophils. CD4:CD8 ratio is variable. There also a good number of CD30 positive reactive B-immunoblasts.

Diagnostic algorithms in CD3 positive T-cell rich lesions in the mediastinum: Problems in diagnosis is usually encountered in needle core biopsies from mediastinum. The differential diagnosis in such a lesion includes T-ALL/LBL and thymoma-type B1. Work-up should include CD4, CD8, CD5, broad range keratin and TdT. The phenotype of the lymphoid cells is similar in both lesions – positive for TdT, CD3, CD5, CD4 and CD8. However, the keratin stain highlights the intricate network of the dendritic epithelial cells in thymoma, type B1, which is lacking in T-ALL/LBL. It should be noted that occasional epithelial cells or parts of Hassall's corpuscle can be present in biopsies from T-ALL/LBL.

Suggested readings:

1. Borowitz MJ abd Chan JKC. T lymphoblastic leukaemia/lymphoma. in Swerdlow SH, Campo E,

Harris NL et al (ed): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC, 2008, pp 176-178

2. Gaulard P, Jaffe ES, Krenacs L, Macon WR. Hepatosplenic T-cell lymphoma. in Swerdlow SH, Campo E, Harris NL et al (ed): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC, 2008, pp 292-293.

3. Attygalle AD, Chuang SS, Diss TC, Du MQ, Isaacson PG, Dogan A. Distinguishing angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified, using morphology, immunophenotype and molecular genetics. Histopathology. 2007 Mar;50(4):498-508.

4. Pileri SA, Weisenburger DD, Sng I et al. Peripheral T-cell lymphoma, nototherwise specified. in Swerdlow SH, Campo E, Harris NL et al (ed): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC, 2008, pp 306-308.

5. Ralfkiaer E, Willenze R, Paulli M, Kadin ME. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders. in Swerdlow SH, Campo E, Harris NL et al (ed): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC, 2008, pp 300-301.

6. Jaffe ES, Gaulard P, Willenze R, Cerroni L, Meijer CJLM. Subcutaneous panniculitis-like T-cell lymphoma. in Swerdlow SH, Campo E, Harris NL et al (ed): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC, 2008, pp 294-295.

7. Chan JKC, Quintanilla-Martinez L, Ferry JA, Peh S-C. Extranodal NK/T-cell lymphoma, nasal type. in Swerdlow SH, Campo E, Harris NL et al (ed): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC, 2008, pp 285-288.

Diagnostic Challenges in Grey Zone Lymphomas

The principal aim of the lymphoma classification is to identify distinct lymphomas with characteristic morphology, immunophenotype, genetic features, clinical presentation and behavior. However, a proportion of lymphomas do not conform to these definitions. By contrast, these have morphology, immunophenotype, genetic features or clinical features that overlap one or more lymphoma types and are referred as 'grey zone' lymphomas.

The 2008 World Health Organization (WHO) classification of tumours of hematopoietic and lymphoid tissues recognizes this problem and has introduced two provisional categories of B cell lymphoma, unclassifiable, one with features intermediate between diffuse large B cell lymphoma (DLBCL) and Burkitt lymphoma (BL) and the second with features intermediate between DLBCL and classical Hodgkin lymphoma (cHL).The grey zone category not specified in the WHO classification includes cases with features overlapping between nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B cell lymphoma (THRLBCL).

Before considering the 'grey zones', it is important to review in brief the distinctive features of the two ends of the spectrum for each of the 'grey zone' lymphoma - BL, DLBCL, primary mediastinal large B-cell lymphoma (PMLBL), cHL, NLPHL and THRLBCL.

Burkitt lymphoma: Three clinical forms of BL are recognized - the endemic form, the sporadic or non-endemic form, and the immunodeficiency-related form (mostly HIV-associated). The endemic form, typically seen in sub-Saharan Africa is generally found in boys under the age of 10 years involving the jaw or the abdomen, and is Epstein Barr virus (EBV) positive in 100% of the cases. The non-endemic form is observed in the rest of the world and affects boys between the ages of 5 and 15 years, often presenting in the ileocaecal region, but extranodal locations including meningeal and bone marrow are not uncommon. The HIV-associated form is predominantly nodal. EBV-association is present in 20–30% of non-endemic and HIV-associated cases. Morphologically, BL cells are cohesive and have a starry-sky pattern. The cells have deeply basophilic cytoplasm with lipid vacuoles (appreciated in cytological preparations). The nuclei are intermediate in size and are round with finely clumped chromatin and multiple medium-sized paracentral nucleoli. Some variation in nuclear size and other nuclear features, including presence of larger central nucleoli may be seen in some cases. Some of these 'atypical' cytological features can be attributed to artefacts introduced by suboptimal tissue preservation and fixation. On immunohistochemistry, BL cells express CD20, CD10, BCL6, CD77, CD38 and surface IgM without IgD, and they lack expression of BCL2 and TdT (always). MUM1 may be expressed in some cases. The characteristic genetic abnormality of

BL is the balanced chromosomal translocation involving one of the immunoglobulin genes (IG) and the MYC gene without any other cytogenetic abnormality or with a very limited number of additional aberrations (MYC-simple). In most cases, IGH is the translocation partner, whereas in approximately 15% of the cases IGL or IGK partner the MYC. Although fluorescent in situ hybridization (FISH) analysis can detect these abnormalities, genetic complexity, a feature important for disease classification cannot be adequately addressed without conventional karyotyping or comparative genomic hybridization (CGH).

Diffuse large B-cell lymphoma: DLBCL represents ~40% of all adult non Hodgkin lymphomas (NHL), and 10–20% childhood NHLs in most developed countries. It is well recognized that based on clinical presentation, morphology, phenotype and molecular genetics, DLBCL is heterogeneous. In DLBCL, translocations involving 8q24/MYC is seen in 5–15% of the cases, and they have a relatively poor outcome. Usually, such cases have complex karyotype and many have MYC translocation involving non-IG partners.

Primary mediastinal large B-cell lymphoma: PMLBL often presents as a rapidly enlarging mediastinal mass in young women. The tumour is composed of an infiltrate of large cells with round or lobulated nuclei, and abundant clear cytoplasm. Occasional atypical cells resemble Hodgkin cells and few multilobated or multinucleated cells may resemble RS cells. There is often a characteristic background compartmentalizing sclerosis. A proportion of cases may show nodularity and necrosis causing superficial mimicry to cHL of nodular sclerosis type (NSHL). The cells show strong expression of CD45, CD20, CD79a and PAX5, and B-cell-associated transcription factors OCT-2 and BOB.1. They however,

lack immunoglobulin (Ig) expression. CD30 of variable intensity is expressed in most cases, and CD15 and EBV association are characteristically negative. Most cases express CD23, which is a useful diagnostic feature. The cells are variably positive for CD10 and BCL6. Unlike other DLBCLs, TRAF-1 and cREL are expressed in PMLBL, and reflects activation of the nuclear factor kappa B pathway. PMLBL has characteristic genetic abnormalities that include chromosomal gains at 9p13.1–9p13.3 (~70%), 9p23-p24 (~60%), and 2p15- p16.1 (involving REL and BCL11A; ~60%), and chromosomal loss at 1p13.1-p13.2 (~40%). On gene expression profiling, PMLBL has features distinct from DLBCL and is more akin to cHL. The expressed genes include MAL, CD23, FIG1, TARC, NFkB2, and PDL1/L2. In routine diagnostic practice, expression of CD30 and CD23 in combination with characteristic morphology including compartmentalizing sclerosis and clinical presentation are helpful in arriving at the diagnosis of PMLBL.

Classical Hodgkin lymphoma: The characteristic feature of cHL is presence of a minority of neoplastic cells amidst an overwhelming majority of benign reactive infiltrate. The neoplastic cells apart from possessing the typical cytological features express CD30 and frequently express CD15 (~80%). In about 20-40% cases B-cell molecules CD20 or CD79a are expressed. Typically, the expression of CD20 and CD79a in cases positive for these molecules is weak and present in only a proportion of cells. The B-cell nature of the neoplastic cells is revealed by the expression of B-cell transcription factor PAX5, which is typically weak. The abnormal B-cells do not express Ig and CD45, and most cases do not show concomitant expression of the transcription factors OCT-2 and BOB.1. EBV-association is variable, with ~25%

being positive in the developed world and >70% cases being positive in developing countries.

Nodular lymphocyte predominant Hodgkin lymphoma: NLPHL is an uncommon disease accounting for about 5% of all cases of HL in Western countries. It is characterized by a nodular / large-follicular pattern and neoplastic proliferation of abnormal large B-cells (popcorn cells) that are currently termed lymphocyte predominant cells (LP cells), in a germinal centre-like microenvironment. NLPHL typically affects adults in third to fifth decades of life, and has an indolent clinical course with fairly frequent relapses. NLPHL involves peripheral nodes and unlike cHL, mediastinal and splenic involvement are rare. Recurrences of cHL usually show features of cHL, whereas recurrences of NLPHL can be show either NLPHL or represent transformation to a large B-cell lymphoma. In approximately, in 3-7% patients with NLPHL, concurrent or subsequent transformation to a DLBCL or THRLBL is observed. The nodules of NLPHL represent transformed abnormal germinal centres and appropriate markers (CD21, CD23 or CD35) highlight the FDCs. The neoplastic large cells express CD45, CD20, CD79a, BCL6, OCT2 and BOB.1. They are often positive for EMA and J-chain (Ig). They are mostly negative for CD30 and always negative for EBV and CD15. The small lymphoid cells present within the nodules represent B-cells with a mantle zone phenotype (IgM & IgD positive) and follicular T-cells (positive for CD3, CD4, CD57 and PD-1). Rosetting of the large neoplastic cells by these T-cells best demonstrated by PD-1 is a useful feature for diagnosis.

T-cell/histiocyte rich B-cell lymphoma: THRLBL represents a variant of DLBCL characterized by a diffuse

pattern and presence of neoplastic CD20 positive B-cells with features of centroblasts, immunoblasts, LP cells and cells resembling RS cells, which account for less than 10% of the infiltrate and are scattered among a majority of non-neoplastic T-cells with or without histiocytes. Follicular dendritic cells or a follicular pattern is not demonstrable with appropriate immunostains. The immunophenotype of the large B-cells is similar to those in NLPHL, but the background non-neoplastic small lymphoid cells are mostly CD3 and CD8 positive.

B cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL:

Separation of BL and DLBCL is critical as optimal treatment for these two entities differ and treatment decisions will have a major impact on patient outcome. However, in the following situations distinction between DLBCL and BL is blurred and a diagnosis of 'grey zone' lymphoma is warranted.

DLBCL with features akin to BL: In less than 10% DLBCLs, a differential diagnosis of BL is considered. Such cases may have a cohesive growth pattern in the absence of a stromal reaction or an admixture with reactive T cells, or have numerous mitoses and apoptoses along with a starry-sky pattern. As a rule-of-thumb, cases with definite large cell cytology, showing 'empty' vesicular nuclei, multiple large nucleoli or abundant cytoplasm should be classified as DLBCL, irrespective of the immunophenotype. In DLBCLs with features akin to BL, translocations involving 8q24/MYC is seen in up to 40% cases. These cases often have a complex karyotype with MYC translocation involving non-IG partners. In addition, amplification of MYC, BCL2 or BCL6 genes are seen in some cases. On CGH many of

these cases have more than 6 abnormalities in addition to the MYC translocation (MYC-complex). Presence of MYC-complex karyotype cannot be recognized by standard FISH analysis alone.

Cases with morphological features of BL, but with atypical immunophenotype: A strong BCL2 expression would not be consistent with BL diagnosis, though weak BCL2 expression, possibly due to co-existent EBV-association would be acceptable for BL diagnosis. Lack of BCL6 or CD10 expression would also be inconsistent with BL diagnosis. Cases of otherwise BL, which have Ki-67 expression in <95% cells pose problems. Suboptimal antigen preservation can hamper evaluation of Ki-67 expression. It can be difficult in some cases to ascertain if the Ki-67 expression is 'low' in real-sense or is an artefact.

Cases with morphological and immunophenotypic features of BL, but without demonstrable MYC-translocation: About 10% of all BL that otherwise fulfill the diagnostic criteria have no demonstrable 8q24/MYC breakpoint on FISH analysis. In a proportion of these cases, alterations in MYC may include very small insertions/deletions or breakpoints located far away from the more frequent breakpoint/s and hence would not detectable by FISH. Some of these MYC-translocation-negative cases harbor MYC amplification. Furthermore, unique microRNA changes resulting in MYC up-regulation has been suggested as an alternate mechanism in MYC translocation-negative BLs. Hence, some of the MYC-translocation-negative cases should not ideally placed under the 'grey zone' category, but be diagnosed as true BL following more intense investigations.

'Double-hit' lymphomas: These are characterized by a second translocation in addition to the MYC-IG translocation. The most common translocation is t(14;18) involving the BCL2 gene either as an independent translocation or as a complex translocation on a single chromosome t(8;14;18). However, cases of follicular lymphoma with t(14;18) who later acquire MYC translocation and transform to an aggressive B-cell lymphoma should not be placed under a 'double-hit' lymphoma category. 11q13/CCND1 and 3q27/BCL6 are the additional breakpoints involved in 'double-hit' lymphomas. Rarely, two additional hits may be observed in addition to the MYC translocation, and these are referred as 'triple-hit' lymphomas. These cases show strong expression of CD10, BCL6 and BCL2, and IG expression may be absent. Such lymphomas are more frequent among aggressive lymphomas with features of BL in patients over 60 years of age. Such cases respond poorly to both DLBCL-directed R-CHOP and BL-oriented CODOX-MIVAC regimens.

The problem that 'double-hit' lymphomas pose is the manner in which they are excluded. Currently, most haematopathologists use FISH analysis for commonly involved breakpoints in the analysis of such cases, and as a result identification of 'double-hit' lymphomas would be restricted to the involvement of the investigated breakpoints. By this strategy, cases that may harbor other equally biologically relevant genetic hits would not be classified as 'double-hit' lymphomas. Whether such lesions identified by conventional karyotyping or spectral karyotyping, in an otherwise MYC-translocation-positive BL, should qualify the case to be labeled a 'double-hit' lymphoma is not clear.

Distinguishing BL and DLBCL in adults is of clinical importance as these patients are treated on different chemotherapy regimens – DLBCL on R-CHOP and BL on CODOX-MIVAC. For patients of BL who are inappropriately treated on R-CHOP, the chance of long-term survival is reduced from 80% to <20%. Similarly, patients of DLBCL treated on CODOX-MIVAC may also have suboptimal survival. Optimal treatment for 'true' grey zones cases (between BL and DLBCL) is unclear.

B cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL:

This category mainly pertains to mediastinal lymphomas with features of both DLBCL and cHL. These lymphomas present more commonly in younger males (age: 20–40 years) with mediastinal involvement, although nodal sites outside the mediastinum may also be involved. Both PMBL and NSHL present as localized mediastinal masses in young women. Apart from the morphological overlap of the neoplastic cells, there are genetic and molecular similarities. Though the morphology and the immunophenotype in PMLBL and NSHL are distinctive, in the following situations distinction is blurred and a diagnosis of 'grey zone' lymphoma is warranted.

Some cases have morphology resembling cHL but have atypical features such as presence of sheets of large neoplastic cells, lack of the typical mixed inflammatory/ reactive background. In addition, the immunophenotype of the neoplastic cells tends to be atypical by presence of strong and uniform expression of CD20 and CD45. They tend to express B cell transcription factors like PAX5 (stronger expression than in conventional cHL), OCT-2 and BOB.1. It should be noted that a small proportion of cHL may show strong and uniform expression of CD20,

and this should not be the only criteria to place a lymphoma in the 'grey zone' category. Apart from conventional phenotypic markers of cHL, association with EBV and aberrant expression of T-cell/cytotoxic markers can be helpful in arriving at a diagnosis of cHL in such difficult cases.

Others have morphology more akin to PMLBL with presence of diffuse sheets of monomorphic large cells, with background compartmentalizing sclerosis and a sparse inflammatory background. In some foci the neoplastic cells resemble RS cell or lacunar cells. The immunophenotype tends to be atypical for PMLBL with weak, focal or absent CD20 expression, and expression of CD15 at least focally. Such cases often express B cell transcription factors like PAX5, OCT-2 and BOB.1, though some may show loss of these transcription factors.

In the recent years, a better long term survival for patients with PMLBL has been achieved with MACOP-B, VACOP-B or ProMACE CytaBOM with or without involved field radiotherapy as compared to CHOP (projected 10-year survival 71% vs. 44%). The difference in survival might be smaller between MACOP-B and R-CHOP. A smaller number of patients treated with high dose therapy and stem cell rescue have had long term survival in excess of 80%. In contrast to PMLBL, the treatment of cHL is less ambiguous. Treatment of mediastinal grey zone lymphomas with features overlapping between PMLBL and cHL is unclear.

PMLBL and cHL are known to manifest sequentially or present as composite lymphomas. These are not to termed 'grey zone' lymphomas.

Grey-zone between nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B cell lymphoma (THRLBCL)

This is not recognized as a 'grey zone' in the current WHO classification. The current recommendation is to label a case that otherwise has THRBCL histology, but shows presence of focal NLPHL like area, as 'NLPHL with THRLBCL-like areas'. This is to distinguish such cases from primary THRLBCL whose prognosis is said to be distinctly worse than NLPHL with THRLBCL-like areas. Recognition of the focal NLPHL area can be assisted by CD20, CD21, CD23, PD-1 and IgD immunostains. PD-1 positive follicular T-cells typically rosette the neoplastic cells in NLPHL. Similarly, localization of neoplastic cells within FDC meshworks as defined by CD21/CD23 immunostains is very helpful for identifying NLPHL areas.

Patients of NLPHL and NLPHL with THRLBCL-like areas are treated with involved field radiotherapy or with chemotherapy regimens similar to cHL. More recently, addition of rituximab has been tried in some clinical trials in both treatment-naive and relapse settings. In contrast, patients of de novo THRLBCL are treated similar to DLBCL on R-CHOP with or without radiotherapy. Distinguishing typical NLPHL, NLPHL with THRLBCL-like areas and de novo THRLBCL is virtually impossible in needle core biopsies, and it should be thoroughly discouraged.

In addition to the 'grey zones' discussed, one may infrequently encounter cases with features overlapping between cHL and THRLBCL, cHL and NLPHL, cHL and 'peripheral' T-cell lymphomas, THRLBCL and 'peripheral' T-cell lymphomas, and among various EBV-associated

large B-cell proliferations occurring in immune deficiency states or in the elderly. Such cases need extensive immunohistochemistry and molecular/cytogenetic work-up, and a proportion of them are resolvable, while others may remain unclassified.

References:

1. Kluin PM et al (2008) B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. In: Swerdlow SH et al (eds) WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, IARC, pp 265–266.
2. Bea S et al (2005) Diffuse large B-cell lymphoma subgroups have distinct genetic profiles that influence tumor biology and improve gene-expression-based survival prediction. Blood 106:3183–3190.
3. Lim MS et al (2002). T-cell/histiocyte-rich large B-cell lymphoma: a heterogeneous entity with derivation from germinal center B cells. Am J Surg Pathol;26:1458-1466.
4. Dave SS et al (2006) Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 354(23):2431–2442.
5. Gaulard P et al (2008) Primary mediastinal (thymic) large B-cell lymphoma. In: Swerdlow SH et al (eds) WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, IARC, pp 250–251.

Basic Minimal Immunohisto-chemistry and Molecular Panel for a Hematopathology Laboratory. Evidence (opinion) Based Approach to Hematolymphoid Neoplasms

Lymphoma diagnosis involves integration of results of several modalities of investigation – morphology, immunohisto-chemistry (IHC), flow cytometry (FCM), cytogenetics and molecular diagnostics, in the context of clinical presentation and imaging investigations. A good quality paraffin embedded hematoxylin and eosin (H&E) stained section and IHC remains cornerstone of diagnosis of a hematolymphoid malignancy. WHO classification subtypes hematolymphoid neoplasms into myeloid neoplasms, precursor lymphoid neoplasms, mature B cell neoplasms, mature T- and NK- cell neoplasms, Hodgkin lymphoma (HL), immunodeficiency associated LPD, histiocytic and dendritic cell neoplasms.

Various IHC and molecular markers have been proposed in the literature as a part of the diagnostic panel. Based on above categories and protocols, we propose a panel of markers which may help further categorize hematolymphoid neoplasms so as to make therapeutic

decisions. This is an opinion/experience based minimal panel. We present list of minimal as well as preferable number of antibodies and molecular markers for a hematopathology laboratory.

A. List of minimal antibodies (IHC) for a hematopathology laboratory:

LCA, CD3, CD20, CD15, CD30, ALK-1, Cyclin D1, CD5, CD23, CD10, bcl2, Mib 1, CD138, kappa and lambda light chains, Tdt, CD34, Anti MPO, CD56

B. List of minimal molecular markers for a hematopathology laboratory:

1. t(8;14)(q24;q32), t(8;22)(q24;q11). – cMYC translocation studies, for cases which are close differential between BL and DLBCL (intermediate unclassifiable category).
2. T-cell receptor gene rearrangement, gamma/beta chains for T cell clonality-PCR
3. IgH gene rearrangement for B cell clonality by PCR

C. Comprehensive list of antibodies (IHC) so as to constitute a good hematopathology practice.

In addition to CD20 and CD3, following are the minimal essential makers for common hematolymphoid neoplasms. In an ideal situation markers suggested within brackets are also employed (for nodal and extranodal sites). It includes various diagnostic, prognostic as well as predictive markers.

1. Follicular hyperplasia vs. Follicular lymphoma: bcl2, CD23, Mib1, IgD (CD10, BCL6, cyclin D1 & light chains)

2. Small B-cell lymphoma (LN): CD5, CD10, CD23, BCL6, BCL2, cyclin D1 & Ki67 (MUM1, CD43, CD38, P53, IgM, IgD & light chains)
3. DLBCL: Ki-67 (CD10, BCL6, MUM1, BCL2, cyclin D1, CD5, EBER (ISH), P53, Tdt, CD44, CD38 & light chains)
4. BL: CD10, BCL6, BCL2 & Ki-67 (MUM1, cyclin D1, CD5, EBER (ISH), P53, Tdt, CD44 & CD38)
5. Plasma cell dyscrasias: CD138 & light chains, CD20 (CD79a, EMA, CD56, cyclin D1, CD117, Mum1)
6. B-LL: Tdt, CD79a, CD20, PAX5 & CD10 (CD34, myeloperoxidase, CD117 & Ki-67)
7. T-LL: Tdt (CD1a, CD34, MPO, CD56, CD4, CD8, Ki-67, CD10, CD79a & PAX5)
8. Node based T-cell lymphoma (other than T-LL): CD45, CD2, CD5, CD7, CD4, CD8, CD10, CD21, CD56, CD30, CD15, ALK-1, EBER & perforin/ granzyme B (CXCL13, PD1 & light chains)
9. ALCL: CD30, ALK, CD15, PAX5, CD79a, CD43, CD2, CD5, CD7, CD8, broad range keratin, Melan A & EMA (IgA, perforin, granzyme B, EBER & Ki-67)
10. HL: CD45, CD15 & CD30 (PAX5, OCT2, BOB.1, CD21, MUM1, CD4, CD8, CD57, BCL6, EBV-LMP1/EBER (ISH), J-chain, IgM, light chains & EMA)
11. Myeloid sarcoma: CD45, CD43, MPO, CD34, CD10, TdT, CD117 & CD68R (CD33, HLADR, Glycophorin C, CD42b or CD61, mast cell tryptase, PAX5, CD79a, CD2, CD5, CD7, CD4, CD8, CD56, CD123 & CD13)

12. Natural killer (NK) cell lymphoma: CD5, CD7, CD4, CD8, CD56, EBER & peforin/granzyme B (CD16, CD57, Ki-67, ALK, CD30 & CD123)
13. Cutaneous lymphomas: CD4 & CD30 (CD8, CD20, bcl 2, bcl 6, bcl 10, Tdt, CD43, CD56)

D. Comprehensive list of molecular markers so as to constitute a good hemato-pathology practice: Kindly refer the test "WHO 2008 classification of hematolymphoid neoplasms" for an extensive list of markers.[1]

E List of IHC markers for a BM trephine biopsy in a suspected lymphoproliferative disorder

It is important to use predetermined antibody panels rather than individualize for each case. In addition to CD20 and CD3, the following are the minimal essential markers for common conditions. In an ideal situation markers suggested within brackets are also employed.

Good quality hematoxylin and eosin stained slide is still the gold standard for diagnosis of a hematolymphoid neoplasm. Optimal tissue processing should be of utmost priority to any hematopathology laboratory.

1. Small B-cell proliferations: CD5, CD10, CD23, cyclin D1 & DBA44 (CD21, MUM1, CD38, P53, CD25, TRAP, BCL3, CD11c, CD68R, vs38C, IgM, IgD & light chains)
2. 'High-grade' B-cell proliferations: CD10, BCL6, BCL2 & Ki-67 (MUM1, cyclin D1, CD5, EBER (ISH). P53, Tdt, CD44 & CD38)
3. Plasma cell dyscrasias: CD138, kappa and lambda light chains (CD79a, CD20, EMA, CD56, cyclin D1, CD117)

4. B-ALL: Tdt, CD79a, PAX5 & CD10 (CD34, myeloperoxidase, CD117 & Ki-67)
5. T-ALL: Tdt (CD1a, CD34, myeloperoxidase, CD56, CD4, CD8, Ki-67, CD10, CD79a & PAX5)
6. Small T-cell proliferations (other than T-LL): CD2, CD5, CD7, CD4, CD8, CD25, CD56, CD57, & perforin / granzyme B (TCR-beta, CD30, FOXP3 & EBER)

References:

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileris SA, Stein H, Thiele Jj, Vardiman JW. WHO Classifications of Tumors: Tumors of Hematopoietic and Lymphoid Tissues; Fourth Edition. WHO Classification of Tumor, Volume 2, IARC WHO Classification of Tumors, No 2, 2008
2. Neoplastic Hematopathology. 2nd Edition. Lippincott Williams & Williams, Ed. Daniel Knowles.
3. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, Eighth Edition.* 978-0-7817-7207-5 Authors: Vincent T. DeVita, Jr., M.D., Theodore S. Lawrence, M.D., Ph.D. , Steven A. Rosenberg, M.D., Ph.D.
4. Principles and Practice of Pediatric Oncology (Hardcover). by Philip A Pizzo (Author), David G Poplack.
5. Naresh KN, Srinivas V, Soman CS: Distribution of various subtypes of non-Hodgkin's lymphoma in India: a study of 2773 lymphomas using R.E.A.L. and WHO Classifications. Ann Oncol 2000;11 Suppl 1:63-7
6. Craig FE, Foon KA. Flow cytometric immunophenotyping for hematologic neoplasms.

Blood. 2008 Apr 15;111(8):3941-67. Epub 2008 Jan 15

7. Gujral S, Subramanian PG, Patkar N, Badrinath Y, Kumar A, Tembhare P, Vazifdar A, Khodaiji S, Madkaikar M, Ghosh K, Yargop M, Dasgupta A. Report of proceedings of the national meeting on "Guidelines for Immunophenotyping of Hematolymphoid Neoplasms by Flow Cytometry". Indian J Pathol Microbiol. 2008 Apr;51(2):161-6

8. Chan WC, Fu K. Molecular diagnostics on lymphoid malignancies. Arch Pathol Lab Med. 2004 Dec;128(12):1379-84. Review

9. Naresh KN, Lampert I, Hasserjian R, Lykidis D, Elderfield K, Horncastle D, Smith N, Murray-Brown W, Stamp GW. Optimal processing of bone marrow trephine biopsy: the Hammersmith Protocol. J Clin Pathol. 2006 Sep;59(9):903-11. Review

Selected Abstracts

1. The 2008 World Health Organization classification system for myeloproliferative neoplasms: order out of chaos.

Tefferi A, Thiele J, Vardiman JW.

Cancer. 2009 Sep 1;115(17):3842-7.

The first formal classification of chronic myeloid neoplasms is credited to William Dameshek, who in 1951 described the concept of "myeloproliferative disorders (MPD)" by grouping together chronic myelogenous leukemia, polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The 2001 World Health Organization (WHO) classification of myeloid malignancies included these

MPDs under the broader category of chronic myeloproliferative diseases (CMPD), which also included chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES), and "CMPD, unclassifiable." The revised 2008 WHO classification system featured the following changes: 1) the term "CMPD" was replaced by "myeloproliferative neoplasm (MPN)," 2) mast cell disease was formally included under the category of MPN, and 3) the subcategory of CEL/HES was reorganized into "CEL not otherwise specified (CEL-NOS)" and "myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, and FGFR1"; CEL-NOS remained a subcategory of "MPN," whereas the latter neoplasms were now assigned a new category of their own. Furthermore, diagnostic criteria for PV, ET, and PMF were revised by incorporating recently described molecular markers (eg, JAK2 and MPL mutations) as well as underscoring the role of histology in differentiating reactive from clonal myeloproliferations. As a result, red cell mass measurement is no longer necessary for the diagnosis of PV, and ET can now be diagnosed at a lower platelet count threshold. The revised WHO document continues to promote the recognition of histologic categories as a necessary first step toward the genetic characterization of myeloid malignancies.

2. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes.

Vardiman JW, Thiele J, Arber DA, et al.

Blood. 2009 Jul 30;114(5):937-51. Epub 2009 Apr 8.

Recently the World Health Organization (WHO), in collaboration with the European Association for Haematopathology and the Society for Hematopathology, published a revised and updated edition of the WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissues. The 4th edition of the WHO classification incorporates new information that has emerged from scientific and clinical studies in the interval since the publication of the 3rd edition in 2001, and includes new criteria for the recognition of some previously described neoplasms as well as clarification and refinement of the defining criteria for others. It also adds entities-some defined principally by genetic features-that have only recently been characterized. In this paper, the classification of myeloid neoplasms and acute leukemia is highlighted with the aim of familiarizing hematologists, clinical scientists, and hematopathologists not only with the major changes in the classification but also with the rationale for those changes.

Indications and Time Points for PET-CT in Diffuse Large B-cell NHL

Conventional imaging of lymphoma has been performed with computerized Tomography. Magnetic Resonance Imaging is being evaluated in some countries. Ultrasound is also used for regional imaging and guiding Biopsy or fine needle aspirations. Flouro -de-oxy Glucose (FDG) Positron emission Tomography (PET) has made a significant impact in Lymphoma imaging.

Initial diagnosis

There is very limited role of FDG PET in initial diagnosis as definitive histopathology is required. However it has been used to select an ideal site for biopsy. This remains a potential utility of FDG PET.

FDG PET/CT for staging of Lymphoma:

The whole body FDG PET/CT has a sensitivity of 99.2% and specificity of 100% in the diagnosis of nodal disease compared to 83% and 99% of CECT. Baseline PET is the reference study for the future PET studies, besides being a prognostic indicator. The baseline SUV (standardized uptake value) has been found to be a prognostic indicator. Prediction of aggressiveness of

histology seen with higher SUV more than 7 in staging of primary lymphoma.

Combined PET and low-dose, noncontrast CT scanning obviates the need for additional diagnostic contrast-enhanced CT scans in patients undergoing staging or restaging for lymphoma. Integrated FDG PET/CT is superior to conventional lymphoma staging procedures – Gallium scanning, CECT or FDG PET alone.

FDG based lymphoma staging is robust and has a high interobserver agreement. It is also useful in the staging of childhood lymphoma.

Bone Marrow biopsy (BMb) and FDG-PET are complementary in the evaluation of Bone marrow Disease (BMD). FDG-PET improves the sensitivity of BMb, especially in the presence of focal BMD. Performing FDG-PET before BMb is advised for optimal biopsy site targeting

For initial staging of splenic involvement in malignant lymphoma, the sensitivity and specificity of PET/CT can reach 100% and 95%. The sensitivity of the combined approach is higher than that of either technique alone.

FDG PET/CT for interim evaluation for treatment response:

Evaluation of metabolic response with FDG PET/CT after 2-3 cycles of chemotherapy is interim evaluation. This is expressed qualitatively or quantitatively as response ratio or indices. Assessing interim response using PET can stratify responders and non-responders. Current evidence suggests that early responders have better prognosis. Even in pediatric Hodgkin's lymphoma this has been ratified by a prospective trial.

However the NCCN recommends interim evaluation with PET only in a protocol setting.

FDG PET/CT for end treatment evaluation

FDG PET has a high negative predictive value in this setting. Evaluation of disease activity by FDG PET in residual masses seen on CT scan offers an incremental benefit.. A negative FDG PET in the end treatment evaluation has high negative predictive value and a recognized favorable prognostic indicator of long time disease free outcome. PET has a positive predictive value of 60-100% and negative predictive value of 80-100%, compared to 19%-60% & 50% - 70% for CECT. A negative PET scan demonstrated 87-100% survival after 1 year and 80-90% after 2 years.

FDG PET before Bone marrow transplant

FDG PET is recommended before transplant evaluation because of its high power of prognostication. A negative Pre BMT study is seen to be associated with progression free survival .

FDG PET evaluation in the follow-up of lymphomas

FDG PET is useful in the followup of NHL patients.

A large prospective study performed recently to study the impact of FDG PET in the disease follow-up. Following complete remission 421 patients were evaluated with serial FDG PET at 6, 12,18, 24 months. Only 33% of the cases that picked a relapse on PET showed a CT lesion or finding to suspect a relapse. . FDG PET is associated with a high negative predictive value ,high sensitivity but a significant false positive rate..

Ultrasound guided biopsy appears to be an effective method of evaluating suspected metabolically active lesions seen in followup scan

Level of Evidence:

Time of FDG PET	Health Technology Approach - Level	Relevance of Appropriateness criteria	Levels of evidence based on type of study (oxford) "Diagnosis"
Diagnosis	Level 1	Potentially appropriate – site of biopsy	NIL
Staging	Level 4	appropriate	Level1
Interim PET	Level 4	appropriate	Level1
End treatment evaluation	Level4	appropriate	Level1
Pre BMT	Level3	appropriate	Level1
Follow-up	Level3	appropriate	Level1

References:

1. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nucl Med. 2010 Jan;51(1):25-30. Epub 2009 Dec 15.
2. Expert opinions on positron emission tomography and computed tomography imaging in lymphoma.Oncologist. 2009;14 Suppl 2:30-40.
3. Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med. 2008 Mar;49(3):480-508. Epub 2008 Feb 20.
4. FDG-PET in the detection of bone marrow disease in Hodgkin's disease and aggressive non-Hodgkin's lymphoma and its impact on clinical management. Q J Nucl Med Mol Imaging. 2008 Mar;52(1):9-16.

5. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin's lymphoma.

   Ann Oncol. 2010 Jan;21(1):126-32. Epub 2009 Jul 16.

6. Early and late therapy response assessment with [18F]fluorodeoxyglucose positron emission tomography in pediatric Hodgkin's lymphoma: analysis of a prospective multicenter trial.

   J Clin Oncol. 2009 Sep 10;27(26):4385-91. Epub 2009 Aug 10.

Selected Abstracts:

1. Interim fluorodeoxyglucose positron emission tomography for early response assessment in diffuse large B cell lymphoma: where are we now?

Leuk Lymphoma. 2009 Dec;50(12):1931-6.

Fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been established in response assessment after treatment of diffuse large B cell lymphoma (DLBCL) and has been incorporated in the International Workshop Criteria (IWC). Early response assessment is increasingly being used in trials and clinical practice with the hope that it has a greater power to discriminate between good and poor prognosis patients at an earlier point in time. Early data have been very promising and suggest that PET after two to three cycles predicts progression-free survival with high accuracy. Early prediction of prognosis has the potential of enabling early treatment tailoring according to the

individual prognosis. Studies are yet to be done to examine the effect of changing therapy early on the basis of poor metabolic response. However, the prognosis of responders/non-responders has been different in various studies, with few recent studies casting some doubt on the value of interim PET. Some of these differences are due to variability in patient populations and treatment protocols. However, there are also important factors related to the methodology of PET scanning and the criteria used to assess response. There is a need for a consensus on a uniform methodology for the use of interim PET both in clinical trials and routine clinical practice. This article critically reviews the current status and suggests future questions for further research.

2. PET/CT for therapy response assessment in lymphoma.

J Nucl Med. 2009 May;50 Suppl 1:21S-30S. Epub 2009 Apr 20.

PET with (18)F-FDG is a standard staging procedure for most lymphoma subtypes. Performed during and after therapy for Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma (NHL), (18)F-FDG PET results have a high prognostic value and correlate with survival. (18)F-FDG PET has been incorporated into revised response criteria for aggressive lymphomas, and several ongoing trials are under way to investigate the value of treatment adaptation based on early (18)F-FDG PET results for HL and aggressive NHL. There is little evidence to support the use of (18)F-FDG PET for monitoring of the treatment of indolent lymphomas and for routine use in the surveillance setting. So that trial results can be compared and translated easily into clinical practice,

uniform and evidence-based guidelines for the interpretation and reporting of response monitoring scans are warranted. Because it is still not proven that the use of interim (18)F-FDG PET can improve patient outcomes, we recommend examination of the use of (18)F-FDG PET for response monitoring in appropriately designed clinical trials.

3. Positron emission tomography using F-18 fluorodeoxyglucose pre- and post-autologous stem cell transplant in non-Hodgkin's lymphoma.

Bone Marrow Transplant. 2008 Jun;41(11):919-25. Epub 2008 Apr 7.

Positron emission tomography (PET) utilizing fluorodeoxyglucose (FDG) has an ever-increasing role in the management of numerous malignancies. FDG PET in lymphoma is being incorporated into the response assessment in lymphoma as published by the Imaging Subcommittee of International Harmonization Project in Lymphoma. The exact role of FDG PET in non-Hodgkin's lymphoma (NHL) associated with autologous stem cell transplant (ASCT) is unclear. Numerous studies have identified pretransplant PET scans as being highly prognostic with regard to overall and PFS after ASCT. Many included a wide range of histologies, including Hodgkin's lymphoma and NHL. In studies with mixed histologies, PFS at 2 years has been improved by as much as 82% in patients with negative pre-ASCT PET scans. In studies incorporating only patients with NHL, improvements in failure-free survival have been reported as high as 43% for patients with negative pre-ASCT PET imaging. Limitations have included inclusion of many histologies, different reported time points, small

retrospective studies and variation in the interpretation of a positive PET. Validation is ongoing in larger prospective trials. Future directions include the potential incorporation of post-ASCT therapy, such as radiation therapy or maintenance antibody therapy, for patients with positive pre-ASCT PET scans.

4. **"Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma." Zinzani, P. L., V. Stefoni, et al. (2009).**

   J Clin Oncol 27(11): 1781-1787.

PURPOSE: In lymphoma, [(18)F]fluorodeoxyglucose positron emission tomography (FDG-PET) is routinely used for initial staging, early evaluation of treatment response, and identification of disease relapse. However, there are no prospective studies investigating the value of serial FDG-PET over time in patients in complete remission.

PATIENTS AND METHODS: All patients with lymphoma who achieved the first complete remission were prospectively enrolled onto the study and scheduled for serial FDG-PET scans at 6, 12, 18, and 24 months; further scans were then carried out on an annual basis. Overall, the population included 421 patients (160 patients with Hodgkin's lymphoma [HL], 183 patients with aggressive non-Hodgkin's lymphoma [NHL], and 78 patients with indolent follicular NHL). All patients had a regular follow-up evaluation, including complete clinical and laboratory evaluation, and final assessment of any suspect FDG-PET findings using other imaging procedures (computed tomography [CT] scan) and/or biopsy and/or clinical evolution. FDG-PET findings were

reported as positive for relapse, inconclusive (when equivocal), or negative for relapse.

RESULTS: PET enabled documentation of lymphoma relapse in 41 cases at 6 months, in 30 cases at 12 months, in 26 cases at 18 months, in 10 cases at 24 months, and in 11 cases at more than 36 months. All 36 patients with inconclusive positive PET underwent biopsy; only 12 (33%) of 36 patients had a concomitant suggestion of positivity on CT. A lymphoma relapse was diagnosed in 24 (66%) of 36 patients. CONCLUSION: Our results confirm FDG-PET as a valid tool for follow-up of patients with HL and NHL. In patients with inconclusive positive results, histologic confirmation plays an important role in identifying true relapse.

Indications and Time Points for PET-CT in Aggressive Non-Hodgkin Lymphoma (Other than Diffuse Large B-cell NHL)

The basic philosophy, indications and the utilities of PET-CT imaging in various types of aggressive non-Hodgkin lymphomas (NHL) in general have evolved in similar lines. Molecular imaging with FDG-PET has been extensively employed in almost every decision making steps in aggressive NHL impacting the initial staging, monitoring therapeutic response both early in the course of therapy and after its completion as well as in the follow-up evaluation of these patients. This has been quite evident in recently published peer reviewed lymphoma literature where the utility of FDG-PET imaging in various subtypes of aggressive NHL have been and are being investigated together in multiple clinical trials.

[A] Value of Early Interim FDG-PET Results in Further Management Decision-Making, Outcome Prediction and Risk Stratification (LOE-IIa):

Of the various decision making utilities of FDG-PET imaging in aggressive NHL, the most promising clinical application has been the early monitoring of response to therapy that has provided a reliable basis of risk stratification and individualizing further treatment based upon the interim FDG-PET imaging results. This has not only provided the oncologists with a simple easy-to-adopt tool for deciding the further course of therapy in an individual but also brought about a paradigm shift in the evidence-based approach in the management of aggressive NHLs in general.

Early identification of non responders to primary chemotherapy by FDG-PET imaging is a major advance in the management of lymphoma since these patients can be moved into the salvage schedules utilizing aggressive strategies at an earlier stage. Newer approaches and chemotherapeutic regimen are being and have been developed based upon this major change or being actively tested in various centres across the world. The recent development of early PET response–adapted further therapeutic decision making has given rise to adopting a number of very promising therapeutic approaches based upon the interim FDG-PET results. These include early escalation to a more intensive regimen like R-ICE (Rituximab + Ifosfamide + Carboplatin + Etoposide) or Burkitt lymphoma regimen or even high-dose therapy with autologous stem cell transplant (ASCT) (NHL) or omitting radiotherapy for patients with interim PET-negative results in patients with mediastinal disease. While the change of therapeutic regimen in non-responders has been based upon convincing evidence, abbreviating chemotherapy or omitting radiotherapy, on the basis of early negative FDG PET results obtained before completion of the planned treatment continues to be considered as an experimental approach.

There is now significant evidence that early PET response even after one to three cycles of chemotherapy may predict ultimate outcome. Several studies have now proven that ^{18}F-FDG PET performed after treatment is highly predictive of progression free survival (PFS) and overall survival (OS) in both HL and aggressive NHL with or without residual masses on CT. The study by Mikhaeel et al demonstrated the prognostic value of early FDG-PET in that the response on ^{18}F-FDG PET after 2 or 3 cycles of treatment strongly predicted PFS and OS in a large, retrospectively studied cohort of 121 patients with high-grade NHL and a median follow-up of 28.5 months. The estimated 5-year PFS rates were 89% for patients with PET-negative results, 59% for patients with minimal residual uptake on ^{18}F-FDG PET, and 16% for patients with PET-positive results. Statistical analysis showed strong associations between early ^{18}F-FDG PET results and PFS and OS. Similar results were obtained in a prospective study by Haioun et al. who studied 90 patients with aggressive NHL, performing ^{18}F-FDG PET after 2 cycles of chemotherapy. The 2-year PFS was found to be 82% and 43% and 2-year overall survival rates to be 90% and 60% in patients with early PET-negative and early PET-positive results, respectively. Spaepen et al. compared interim ^{18}F-FDG PET with the International Prognostic Index. In a multivariate analysis, the prognostic value of early FDG-PET completely overshadowed the role of the International Prognostic Score (IPS) with FDG-PET at midtreatment was found to be stronger predictor for PFS and OS than was the International Prognostic Index. Overall, in aggressive NHL, PFS ranges from 10% to 50% at 1 year for patients with early ^{18}F-FDG PET–positive results and from 79% to 100% at 1 year for patients with early ^{18}F-FDG PET–negative results.

[B] End-of-treatment Response Evaluation with FDG-PET/CT in Aggressive NHL (LOE-1)

FDG PET has the ability to distinguish between viable lymphoma cells and necrosis or fibrosis in residual masses after treatment noted with anatomical imaging modalities. Recently there have been endeavors to incorporate FDG-PET into revised response criteria for assessing treatment response following completion of therapy in aggressive lymphomas in general, replacing the standard International Workshop Criteria and the Cotswold Criteria based mainly on morphologic changes in CT. The revised response criteria is primarily based upon the results of the International Harmonization Project that has developed new recommendations for response criteria for FDG-avid aggressive malignant lymphomas as a whole. However, more clinical data requires to be accrued that may further refine these criteria further.

[C] PET-CT in the follow-up of Lymphoma (LOE-IIb)

A role of FDG-PET has been suggested in the detection of preclinical relapse but these are primarily based upon non-level I evidences. It is opined that this approach will allow initiating salvage therapy with minimal disease rather than overt relapse. A National Comprehensive Cancer Network (NCCN) guidelines and suggestions of provider group suggested end-of treatment restaging PET-CT 4-8 weeks after completion of therapy, every 6 mo for the first 3 years and then annually for year 4 and 5, along with standard follow-up procedures.

[D] FDG-PET/CT for Initial Staging (LOE-I)

Though FDG is a non-specific tracer, the utility of PET/CT has been emphasized for two reasons: (1) a baseline scan forms the basis of evaluation of further treatment response and (2) it is a 1whole body technique, hence provides the disease status in a single examination. Hence, it is presently considered as the cornerstone of staging procedures in the state-of-the-art management of HL and aggressive NHLs. The studies conducted in the initial years of this century demonstrated that the overall sensitivity of PET is on average 15% (range 10-40%) higher than that of CT, whereas the specificity is the same for both imaging modalities. It is expected that fusion imaging with FDG-PET/CT will provide the high sensitivity of ^{18}F-FDG PET with better specificity in assessing the whole body disease burden and will result in better results obtained with PET alone.

Suggested Readings:

1. Basu S. Early FDG-PET response-adapted risk stratification and further therapeutic decision-making in lymphoma: will this replace the established prognostic indices and be the standard-of-care in clinical management? Eur J Nucl Med Mol Imaging. 2009 Oct 28. [Epub ahead of print].
2. Torizuka T, Nakamura F, Kanno T, et al. Early therapy monitoring with FDG-PET in aggressive non-Hodgkin's lymphoma and Hodgkin's lymphoma. *Eur J Nucl Med Mol Imaging.* 2004;31:22–28.
3. Dührsen U, Hüttmann A, Jöckel KH, Müller S. Positron emission tomography guided therapy of aggressive non-Hodgkin lymphomas—the PETAL trial. Leuk Lymphoma. 2009 Nov;50(11):1757-60.

4. Mikhaeel NG, Hutchings M, Fields PA, O'Doherty MJ, Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. *Ann Oncol.* 2005;16:1514–1523.
5. Jerusalem G, Beguin Y, Fassotte MF, et al. Persistent tumor ^{18}F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. *Haematologica.* 2000;85:613–618.
6. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol.* 2007;25:571–578.

Selected Abstracts

1. Positron emission tomography guided therapy of aggressive non-Hodgkin lymphomas—the PETAL trial.

Dührsen U, Hüttmann A, Jöckel KH, et al.

Leuk Lymphoma. 2009 Nov;50(11):1757-60. (LOE 1)

In aggressive non-Hodgkin lymphomas, the result of positron emission tomography(PET) with [18F]fluorodeoxyglucose performed after a few cycles of chemotherapyhas been shown to correlate with long-term treatment outcome. The PETAL trialinvestigates whether a change in treatment protocol may improve the outcome of patients with a positive scan after two cycles of (R-)CHOP. Such patients are randomized to receive a further six cycles of (R-)CHOP or six blocks of

the B-ALL protocol, a regimen for the treatment of Burkitt lymphoma. Precautions taken to minimize false-positive interim-PET results include adherence to a 3-week interval between chemotherapy and interim-PET scanning, avoidance of hematopoietic growth factors, and SUV-based rather than visual interim-PET assessment. So far, 175 patients have been enrolled of whom 128 have reached interim-PET scanning. In patients with a positive scan, relapses were six times more frequent than in patients with a negative scan. Recruitment into the trial continues.

2. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome.

Haioun C, Itti E, Rahmouni A, et al.

Blood. 2005 Aug 15;106(4):1376-81. (LOE 1)

Assessment of early therapeutic response using metabolic imaging is potentially useful to determine prognosis in aggressive lymphoma. Between January 2000 and January 2004, 90 patients with newly diagnosed aggressive lymphoma (median age 53 years, 94% diffuse large B-cell) were prospectively explored with [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) prior to induction chemotherapy, after 2 cycles ("early PET"), and after induction completion. Therapeutic response was evaluated using conventional diagnostic methods at 4 cycles. Induction treatment with an anthracycline-containing regimen was administered to all patients, associated with rituximab in 41%. According to the International Prognostic Index (IPI), 37 patients and 53 patients belonged to the lower- and higher-risk groups, respectively. At midinduction,

"early PET" was considered negative in 54 patients and positive in 36. After completion of induction, 83% of PET-negative patients achieved complete remission compared with only 58% of PET-positive patients. Outcome differed significantly between PET-negative and PET-positive groups; the 2-year estimates of event-free survival reached 82% and 43%, respectively (P < .001), and the 2-year estimates of overall survival reached 90% and 61%, respectively (P = .006). Predictive value of "early PET" was observed in both the lower-risk and higher-risk groups, indicating prognostic independence from the IPI. Therefore, FDG-PET should be an early guide to first-line strategies in aggressive lymphoma.

3. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma.

Spaepen K, Stroobants S, Dupont P, et al.

Ann Oncol. 2002 Sep;13(9):1356-63. (LOE 1)

BACKGROUND: Less than half of all patients with aggressive non-Hodgkin's lymphoma (NHL) are cured with standard chemotherapy. Therefore, it is important to distinguish between responders to standard treatment and non-responders who may benefit from an early change to a more effective therapy. This study was intended to assess the value of a midtreatment fluorine-18 fluorodeoxyglucose positron emission tomography ([(18)F]FDG-PET) scan to predict clinical outcome in patients with aggressive NHL.

PATIENTS AND METHODS: Seventy newly diagnosed patients with aggressive NHL, who were treated with doxorubicin-containing chemotherapy, underwent a

[(18)F]FDG-PET scan at midtreatment. Presence or absence of abnormal [(18)F]FDG uptake was related to progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier survival analysis. Multivariate analysis was performed to evaluate the effect of the International Prognostic Index (IPI) and early [(18)F]FDG-PET findings on PFS and OS.

RESULTS: At midtreatment, 33 patients showed persistent abnormal [(18)F]FDG uptake and none of these patients achieved a durable complete remission (CR), whereas 37 patients showed a negative scan; 31/37 remained in CR, with a median follow-up of 1107 days. Only 6/37 patients either achieved a partial response or relapsed. Comparison between groups indicated a statistically significant association between [(18)F]FDG-PET findings and PFS (P <1 x 10(-5)) and OS (P <1 x 10(-5)). In multivariate analysis, [(18)F]FDG-PET at midtreatment was a stronger prognostic factor for PFS (P <1 x 10(-7)) and OS (P <9 x 10(-6)) than the IPI (P <0.11 and P <0.03, respectively).

CONCLUSIONS: Early restaging [(18)F]FDG-PET may be used to tailor induction chemotherapy in patients with aggressive NHL.

4. **Imaging Subcommittee of International harmonization Project in Lymphoma. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma.**

   Juweid ME, Stroobants S, Hoekstra OS, et al.

   J Clin Oncol. 2007 Feb 10;25(5):571-8. Epub 2007 Jan 22. (LOE 1)

PURPOSE: To develop guidelines for performing and interpreting positron emission tomography (PET) imaging for treatment assessment in patients with lymphoma both in clinical practice and in clinical trials. METHODS: An International Harmonization Project (IHP) was convened to discuss standardization of clinical trial parameters in lymphoma. An imaging subcommittee developed consensus recommendations based on published PET literature and the collective expertise of its members in the use of PET in lymphoma. Only recommendations subsequently endorsed by all IHP subcommittees were adopted.

RECOMMENDATIONS: PET after completion of therapy should be performed at least 3 weeks, and preferably at 6 to 8 weeks, after chemotherapy or chemoimmunotherapy, and 8 to 12 weeks after radiation or chemoradiotherapy. Visual assessment alone is adequate for interpreting PET findings as positive or negative when assessing response after completion of therapy. Mediastinal blood pool activity is recommended as the reference background activity to define PET positivity for a residual mass > or = 2 cm in greatest transverse diameter, regardless of its location. A smaller residual mass or a normal sized lymph node (ie, < or = 1 x 1 cm in diameter) should be considered positive if its activity is above that of the surrounding background. Specific criteria for defining PET positivity in the liver, spleen, lung, and bone marrow are also proposed. Use of attenuation-corrected PET is strongly encouraged. Use of PET for treatment monitoring during a course of therapy should only be done in a clinical trial or as part of a prospective registry.

Evidence based management of Diffuse Large B Cell Lymphoma (DLBCL)

Introduction

Diffuse large B cell lymphomas are the most common lymphomas encountered in clinical practice. They usually occur as localized disease and have a propensity for extranodal involvement.

DLBCL and the international prognostic index

DLBCL are potentially curable neoplasm and their therapy is determined by the five most significant variables (the international prognostic index or IPI) proposed in 1993. These include age, clinical stage, LDH, ECOG performance status and number of extra-nodal sites. The disease is risk stratified into low (0-1 risk factor), low-intermediate (2 factors), high-intermediate (3 factors) and high risk (4 or 5 factors) based on these factors. Each prognostic group show significantly different outcomes, with 5-year relapse-free survival rates ranging from 70% to 40% and overall survival rates ranging from 73% to 26%. An adjustment of the original IPI system

was subsequently developed for less than 60 years (age-adjusted IPI or aaIPI); the risk factors considered were stage, LDH and performance status and risk categories varied from aaIPI 0 to aaIPI 2-3. The IPI or international prognostic index is still considered the best prognosticator for survival in DLBCL and influence the type, intensity, and duration of therapy.

Chemotherapy in DLBCL

Combination chemotherapy for lymphomas was introduced by DeVita in the early 1970s. The regimen, C-MOPP, produced complete responses in about 40% of patients and a third were actually cured. The observation that rapid achievement of CR was associated with good prognosis and that relapses after 2 years of a disease free interval was rare pushed researchers to identify treatment modalities that would give both a rapid and durable remissions. Doxorubicin was added in the mid 70s to cyclophosphamide (CHOP regimen) giving complete responses of 50 to 60% and a DFS of 30 to 40%. Subsequently regimens were developed built around the Goldie and Coldman hypothesis and that of Hryniuk and Bush. The former suggested that tumors develop drug resistance by spontaneous mutation soon after exposure to chemotherapy and the latter proposed that increasing dose intensity could overcome drug resistance. This led to the evolution of the so called 3rd generation regimens which certainly translated into better CRs (78 to 88%) and DFS (58 to 69%) while giving greater toxicity (treatment related mortality of 5 to10%) in the bargain. This toxicity has however decreased with the advent of better supportive care. An intergroup study compared CHOP with three of the newer more intensive regimens, namely, m-BACOD, MACOP-B, and ProMACE . There were no differences in CR, PFS, or

OS. Thus despite all the 3rd generation regimens, CHOP regimen has stood the test of time and remains the most extensively studied and used regimen for DLBCL. (Level of Evidence-II)

Modifications of the CHOP design to improve its efficacy has included both increasing its dose-intensity and dose-density. The dose-intensive ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) regimen, developed by the *Groupe d'Etude des Lymphomes de l'Adult* (GELA) demonstrated an advantage over CHOP in terms of event-free and overall survival (Level of Evidence-I). The CHOEP (CHOP plus etoposide) regimen developed by the German High-Grade non-Hodgkin's Lymphoma (DSHNHL) group proved to be superior to CHOP in young patients with normal lactate dehydrogenase (LDH) (Level of Evidence-II). The dose dense regimen of CHOP 14 (two weekly CHOP) versus CHOP21 (3 weekly CHOP) produced longer survival in young and elderly patients.

Monoclonal antibody therapy in DLBCL

A paradigm shift in the management of DLBCL occurred with the coupling of CHOP chemotherapy with Rituximab, a humanized anti-CD20 monoclonal antibody. The study that showed this improvement in survival was the randomized GELA study comparing CHOP to Rituximab plus CHOP (R-CHOP) in elderly patients (ages 60 to 80 years) with DLBCL. The rate of CR/CRu was higher for R-CHOP compared to CHOP alone (75 vs. 63%). The 5-year EFS and OS were also significantly higher in the R-CHOP arm (47 versus 29% and 58 versus 45% respectively) (LOE - 1). This superiority was evident in patients across all IPI scores. The US E4494 Intergroup trial in the elderly again demonstrated a significant

advantage for patients receiving rituximab, either as part of induction or maintenance therapy. Advantage of adding rituximab to CHOP, in both young and elderly patients with DLBCL, has been categorically confirmed in a large population-based study comparing survival before and after the introduction of rituximab into clinical practice. The British Columbia Cancer Agency observed that in elderly patients the 2-year overall survival improved from 40% to 67% and progression-free survival from 44% to 67%, while in young patients overall survival improved from 69% to 87%, with a 10% gain in the progression-free survival. [LOE - 2]

Another aspect about Rituximab in DLBL is that the IPI prognostic model retains its predictive capacity in patients treated with R-CHOP. A revised IPI (R-IPI) distinguishes three prognostic categories, with differing 4-year survivals ranging from 94% for very good risk (no risk factors) to 79% for good risk (one to two risk factors) and 55% for poor risk (three to five risk factors) subgroups highlights this aspect. However the R-IPI loses out its significance when probability of survival goes below 50%.

Current recommendations for treating DLBCL

Treatment of localized DLBCL

Localized DLBCL may be defined as non bulky (<10cm tumor or no mediastinal mass greater than one third the chest diameter) stage I and II disease. Radiation therapy alone has resulted in 20 to 85% cure rates for this group, with stage I deriving more benefit. However the use of radiation alone in presence of appropriate clinical staging has yielded less than 50% cure. Therefore chemotherapy (CHOP or CHOP like regimens) often followed by

radiation is recommended [LOE - II]. With this approach a cure rates of 70 to 90% is achieved. In a Southwest Oncology Group (SWOG) study, patients with localized intermediate- or high-grade NHL were randomized to three cycles of CHOP followed by involved-field radiation therapy versus eight cycles of CHOP alone. Better PFS (77 vs. 64%) and OS (82 vs. 72%) were observed in the combined-modality arm. The subsequent follow up report however did not indicate better survival. Similarly a GELA trial compared four cycles of CHOP plus RT to CHOP alone in patients >60 years of age and found no difference in EFS or OS. Thus in limited disease one might be able to using chemotherapy alone and achieve comparable results though the chances of local recurrence are much lower when RT is incorporated. Besides the long term toxicity of chemotherapy may be obviated with use of shorter courses of chemotherapy [LOE - II].

Currently it is accepted stage I-II DLBCL with no adverse prognostic factors, i.e. non-bulky disease and IPI equal to 0 should receive abbreviated chemotherapy with an anthracycline-containing regimen plus involved field RT (35-40 Gy) or a full course of chemotherapy alone. Patients with stage I-II disease with one adverse prognostic factor (bulky disease, elevated LDH, performance status ECOG >1) should be treated according to the recommendations for stage III-IV disease.

Therapy for young patients with favourable IPI

There is maximum benefit from incorporating rituximab into chemotherapy which include CHOP or CHOP like regimens in this group. This was clearly brought forth in the MiNT study (Mab-Thera International Trial). The young patient with low risk disease (aaIPI 0-1) receiving

six cycles of R-CHOP21 (or CHOP-like) was superior to CHOP21 (or CHOP-like) therapy, in terms of complete remission (86% *vs.* 68%), failure-free survival (83% *vs.* 53%) and overall survival (95% *vs.* 86%). Significantly different results were obtained according to aaIPI score: in patients with an aaIPI score of 0 and no bulky disease, the time to treatment failure and overall survival rates were 89% and 98%, respectively, whereas in patients with an aaIPI score of 1 and/or bulky disease, the corresponding rates were 76% and 91%, respectively. At the moment, six cycles of R-CHOP21may be considered the standard therapy in low-risk young patients with DLBCL. [LOE - I]

Standard therapy for elderly patients

If the superiority of R-CHOP given every 21 days was shown by the GELA study, the RICOVER 60 trial showed advantage of using R-CHOP as a 14 day schedule in elderly with growth factor support. [LOE - 2]. Their result indicate that six cycles of R-CHOP14 plus eight doses of rituximab significantly improved event-free, progression-free and overall survival compared to six cycles of CHOP14 and that eight cycles of therapy were not better than six. Based on this study R-CHOP14 with growth factor support may be considered as new standard for treating elderly in all IPI categories. However at the same time it must be emphasized that there is no data still out directly comparing R-CHOP14 with R-CHOP21. Studies are ongoing.

The role of CNS prophylaxis in DLBL

The risk of CNS relapse in patients with intermediate-high grade NHL is about 5%, and still higher for high-intermediate/high IPI score. Chemoimmunotherapy does

not reduce the risk of CNS relapses as compared with chemotherapy alone as highlighted in a retrospective study by Bos etal. Specific extranodal sites such as testes, paranasal sinuses, hard palate, orbit, paravertebral masses and the bone marrow are more frequently associated with CNS involvement. Therefore patients with such site involvement are given intrathecal methotrexate as part of CNS prophylaxis along with systemic chemotherapy. Patients with a high-intermediate/high IPI score, particularly reflecting the presence of a high level of LDH and involvement of more than one extranodal site, are at much higher risk than other patients and intrathecal prophylaxis should be incorporated into the systemic regimen for this group.

Summary - management of DLBCL

a. Patients of all ages with stage I-II DLBCL having no adverse prognostic factors, may receive abbreviated chemotherapy with an anthracycline-containing regimen coupled with involved field RT or a full course of chemotherapy (6 cycles)alone. [LOE - I]

b. Patients with stage I-II disease and at least one adverse prognostic factor should be treated according to the recommendations for stage III-IV disease. [LOE - II]

c. Patients with stage III-IV disease should receive frontline chemoimmunotherapy with CHOP, CHOP-like or third-generation chemotherapy plus rituximab. [LOE - I]

d. The use of rituximab as first-line monotherapy is not recommended, except for patients with stage III-IV disease who are, ineligible for chemotherapy. [LOE - II]

e. Patients with stage III-IV disease and bulky disease at diagnosis may receive consolidation involved field RT (30-36 Gy) to the sites of bulky disease. [LOE - II]

f. CNS prophylaxix should be performed in patients with involvement of specific extranodal and in patients with high-intermediate /high IPI score, particularly a high LDH and involvement of more than one extranodal site. [LOE - II]

g. There is no role for maintenance therapy in patients in complete remission after first-line therapy. [LOE - II]

Suggested reading

1. Shipp MA, Harrington DP. The International non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987-94.

2. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993;328:1002–1006.

3. Tilly H, Lepage E, Coiffier B, Blanc M, Herbrecht R, Bosly A, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood 2003;102: 4284-9.

4. Pfreundschuh M, Trümper L, Klöss M, Schmits R, Feller AC, Rudolph C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas. Results of

the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-33.

5. Pfreundschuh M, Trümper L, Klöss M, Schmits R, Feller AC, Rübe C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphoma. Results of the NHL-B2 trial of the DSHNHL. Blood 2004; 104: 634-41.

6. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–242

7. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117–4126.

8. Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121-7 .

9. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 2005;23:5027-33.

10. Pfreundschuh M, Trümper L, Osterborg A, Pettengel R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large B-cell lymphoma: a randomized controlled trial by the Mab-Thera

International Trial (MInT) group. Lancet Oncol 2006;7:379-91.

11. Pfreundschuh M, Shubert J, Ziepert M, Schmits R, Mohren M, Lengfelder E, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomized trial (RICOVER-60). Lancet Oncol 2008;9:105-16.

Abstracts:

1. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group.

Pfreundschuh M, Trümper L, Osterborg A, et al.

Lancet Oncol. 2006 May;7(5):379-91.

BACKGROUND: The role of rituximab in combination with different CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like chemotherapy regimens in young patients with good-prognosis diffuse large-B-cell lymphoma remains to be defined. We aimed to compare CHOP-like chemotherapy and rituximab with CHOP-like chemotherapy alone in these patients.

METHODS: 824 patients who were from 18 countries; aged 18-60 years; and who had no risk factors or one risk factor according to age-adjusted International Prognostic Index (IPI), stage II-IV disease, or stage I disease with bulk were enrolled. These patients were randomly assigned to six cycles of CHOP-like chemotherapy and rituximab (n=413) or to six cycles of CHOP-like chemotherapy alone (n=411). Bulky and

extranodal sites received additional radiotherapy. The primary endpoint was event-free survival; secondary endpoints were response, progression under therapy, progression-free survival, overall survival, and frequency of toxic effects. Analyses were done by intention to treat and per protocol. This trial is registered at http://www.clinicaltrials.gov, NCT 00064116.

FINDINGS: After a median follow-up of 34 months (range 0.03-61), patients assigned chemotherapy and rituximab had increased 3-year event-free survival compared with those assigned chemotherapy alone (79% [95% CI 75-83] vs 59% [54-64]; difference between groups 20% [13-27], log-rank p<0.0001), and had increased 3-year overall survival (93% [90-95] vs 84% [80-88]; difference between groups 9% [3-13], log-rank p=0.0001). Event-free survival was affected by treatment group, presence of bulky disease, and age-adjusted IPI: after chemotherapy and rituximab, a favourable subgroup (ie, IPI=0, no bulk) could be defined from a less-favourable subgroup (ie, IPI=1 or bulk, or both). Groups did not differ in the frequency of adverse events.

INTERPRETATION: Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large-B-cell lymphoma. The definition of two prognostic subgroups allows for a more refined therapeutic approach for these patients.

2. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte.

Feugier P, Van Hoof A, Sebban C, et al.

J Clin Oncol. 2005 Jun 20;23(18):4117-26. Epub 2005 May 2

PURPOSE: To analyze the long-term outcome of patients included in the Lymphome Non Hodgkinien study 98-5 (LNH98-5) comparing cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) to rituximab plus CHOP (R-CHOP) in elderly patients with diffuse large B-cell lymphoma. P

ATIENTS AND METHODS: LNH98-5 was a randomized study that included 399 previously untreated patients, age 60 to 80 years, with diffuse large B-cell lymphoma. Patients received eight cycles of classical CHOP (cyclophosphamide 750 mg/m(2), doxorubicin 50 mg/m(2), vincristine 1.4 mg/m(2), and prednisone 40 mg/m(2) for 5 days) every 3 weeks. In R-CHOP, rituximab 375 mg/m(2) was administered the same day as CHOP. Survivals were analyzed using the intent-to-treat principle.

RESULTS: Median follow-up is 5 years at present. Event-free survival, progression-free survival, disease-free survival, and overall survival remain statistically significant in favor of the combination of R-CHOP ($P = .00002$, $P < .00001$, $P < .00031$, and $P < .0073$, respectively, in the log-rank test). Patients with low-risk or high-risk lymphoma according to the age-adjusted International Prognostic Index have longer survivals if treated with the combination. No long-term toxicity appeared to be associated with the R-CHOP combination.

CONCLUSION: Using the combination of R-CHOP leads to significant improvement of the outcome of elderly patients with diffuse large B-cell lymphoma, with significant survival benefit maintained during a 5-year follow-up. This combination should become the standard for treating these patients.

Radiation Therapy for Nodal High Grade Non-Hodgkin's Lymphoma

Lymphomas in general are very sensitive to ionizing radiation. Radiation therapy (RT) has remained an integral part in the combined modality treatment (CMT) of malignant lymphomas.

Dose of Radiation Therapy When Used Alone

Dose-response data for RT of NHL are sparse. There are no prospective phase III trials addressing this question. Most data come from phase II retrospective analyses.

Pioneering work on RT dose response was done at Stanford University and Princess Margaret Hospital. Fuks and Kaplan in 1973 reported that doses in the range of 44Gy achieved local control of follicular lymphoma (FL) in more than 95% of patients. For diffuse large cell lymphoma (DLCL), local failure rates, however, were in the range of 20% to 30% regardless of the dose of RT delivered.

Investigators from the Princess Margaret Hospital also addressed this issue. Dose-response curves were

constructed for both diffuse large cell lymphoma (DLCL) and FL. For patients with medium- or large-bulk disease, defined as 2.5 to 5 cm in size and more than 5 cm, respectively, an approximately 50% local control rate was achieved with a dose of 20Gy, rising to 70% at 30Gy and 80% at 40Gy with a plateau thereafter, and no apparent improvement with additional dose. For patients with small-volume (<2.5 cm) DLCL, a local control rate >90% was achieved regardless of dose.

Similar data have been reported from the University of Florida. Patients with intermediate & high-grade disease treated with RT alone had local control of >95% with doses of 30 to 50Gy.

Dose of Radiation Therapy in a Combined Modality Treatment Approach

Currently most patients with localized DLCBL and a significant proportion of patients with disseminated disease with associated poor prognostic factors like bulky nodes are treated with CMT approach using multiagent chemotherapy (CTh) and RT.

Literature reports a wide range of RT dose used in a CMT approach. The Vancouver group reported 308 patients with stage I and II DLBCL treated with CHOP (and related combinations) followed by involved field radiotherapy (IFRT) to doses of 30 to 35Gy. The 10-year cause-specific survival rate was 82%. In-field local failures occurred in 3% of patients.

Investigators at the M.D. Anderson Cancer Center examined local control in 294 patients with stages I to IV DLBCL after CHOP-based CTh in a retrospective review. Because of varying dose fractionation schemes, radiation doses were converted using the linear quadratic model

to biologically equivalent doses given at 1.8 Gy per fraction. Patients were then grouped in the 30- to 40-Gy range and 40- to 50-Gy range. Patients were also divided by the size of the primary tumor: <3.5 cm, 3.5 to 10 cm, and >10 cm. For the smallest tumors, doses in the lower dose range provided excellent local control (96%), whereas those patients with tumors from 3.5 to 10 cm at onset had a local control rate of 40% with the lower doses compared with 98% with higher doses. Patients with tumors >10 cm at onset and a CR to CTh had a 5-year local control rate of 70% with a dose of 40Gy. The authors suggested that doses >40Gy might be needed for large tumors.

Krol et al., compared 26Gy versus 40Gy for patients with stage I DLBCL who had achieved a CR to CHOP. There was no difference in outcome for the two doses in this retrospective analysis.

In a study from the Duke University, 45 patients with stage I and II DLBCL treated with CHOP who achieved a CR, defined by anatomic imaging and the presence of a negative gallium scan at the completion of therapy received adjuvant radiation therapy. Doses of RT ranged from 10 to 50Gy but majority received a dose around 30Gy. Long term disease control was achieved in 92% of patients.

Results from studies suggest towards feasibility of dose reduction in malignant lymphomas although there is no phase III data to support the concept.

Radiation Therapy Field Size/Treatment Volume

The optimal treatment volume or field size for RT of localized NHL is also a matter of some controversy

because, as is the case for dose-response information, definitive phase III trials to resolve the issues are not available. Conclusions regarding appropriate field size are extrapolated from information regarding patterns of failure.

For DLBCL, the pattern of failure after CMT is usually disseminated disease, with a small percentage with local failure. After chemotherapy alone, more local failure occurs. A question commonly encountered is the appropriateness of treatment volume/field size after achieving CR after CTh in patients with DLBCL.

In view of the patterns of failure data, treatment of the original volume plus adjacent nodal areas has essentially been abandoned. IFRT was established as the most appropriate field. Whether the involved field should include the pre- or postchemotherapy tumor volume depends a lot on where the original tumor was and the tolerance of surrounding normal tissues. In clinical practice the entire involved nodal region is included in the radiation therapy field, e.g. patients presenting with nodal disease in the neck unilaterally, would receive RT to the entire neck nodes on that side. For a large mediastinal mass which is not infiltrating into the pulmonary parenchyma, the IFRT volume would typically be reduced to encompass the post chemotherapy volume in the lateral dimensions and include the entire vertical extent of the normal mediastinal and hilar structures. Thus it is a regular practice to restrict IFRT to the postchemotherapy volume in situations where excessive dose to normal tissue might result, such as with primary DLBCL of the mediastinum. Similarly for large nodal masses in the retroperitoneal region or pelvic cavity that have responded to chemotherapy and reduced in size, the postchemotherapy volume is usually included in the

transverse dimensions without compromising on the vertical extent of the nodal chain in order to reduce the possibility of nephrotoxicity and urinary bladder and bowel toxicity.

In patients with large residual masses in proximity to critical organs a shrinking field technique can be used where the radiation field size is reduced as the treatment progresses / tumor shrinks and thereby restricting the radiation therapy dose to the nearby critical structures.

Newer radiation therapy techniques like 3 dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) can significantly reduce radiation doses to surrounding normal tissues.

Treatment of Stage I/II Diffuse Large B-Cell Lymphoma,

Historically in the prechemotherapy era, early-stage DLBCL was treated with RT alone. Ten-year failure free survival (FFS) and overall survival (OS) in these series ranged from 30% to 60%. The doses of RT varied widely from 30 to 60Gy. The CR rate was high, usually >80%. Although there was wide variation in the radiation field size, majority were treated using IFRT. The pattern of failure in these series was mostly at sites away from the irradiated volume / primary nodal region. Patients with Stage I & II disease had a long-term FFS and OS in the range of 25% to 60%.

In the late 1970s and early 1980s, efforts to improve on these results by the addition of combination chemotherapy were begun. The results of the early phase III trials involving chemotherapy regimens like CVP (cyclophosphamide, vincristine, prednisone) were not as good as the phase II studies incorporating CHOP. These

latter trials demonstrated a substantial improvement in both FFS and OS with CMT compared to RT alone. CR rates of approximately 90% are reported with FFS and OS in the range of 70% to 85%.

In a phase II trial from the British Columbia Cancer Center, 308 patients with stage I or II disease were treated with CHOP chemotherapy or closely related combinations followed by IFRT. The CR rate was 97%, the FFS was 74% at 10 years, and OS was 63% at 10 years. Radiation doses were 30 to 35 Gy.

Two large cooperative trials from Southwest Oncology Group (SWOG) and Eastern Oncology Group (ECOG) have examined whether chemotherapy alone would suffice for early stage disease. The SWOG trial compared eight cycles of CHOP with three cycles followed by IFRT. Four hundred one patients were entered and evenly divided between the two arms. Majority of patients had a low IPI score. Patients were randomized to receive eight cycles of CHOP or three cycles followed by IFRT. After CHOP, the CR rate was 74% in both arms. Doses of RT ranged from 40 to 55Gy at the discretion of the treating radiation oncologist, with most patients receiving between 45 and 50Gy at a rate of 180 to 200 cGy/day. RT fields usually included the prechemotherapy tumor volume. The 5-year PFS (77% vs. 64%; P = .03) and OS (82% vs. 72%; P = .02) results favored the CHOP and IFRT treatment arm. This trial demonstrated not only that the addition of radiation therapy allowed the use of three cycles instead of eight cycles of CHOP, but also that combined modality therapy using abbreviated chemotherapy resulted in a better outcome than a prolonged course of chemotherapy alone. Additionally, toxicity was greater in the chemotherapy alone arm. The updated results of this

trial reported that at 7 to 9 years there were no longer differences in FFS and OS between the two arms. This was attributed to late relapses and lymphoma deaths beyond 5 years in patients who had received abbreviated CTh followed by IFRT. A subset analysis of the SWOG 8736 trial revealed that patients without any stage-adjusted IPI risk factors had a 5-year OS of 94% after three cycles of CHOP and IFRT. However, in those with one or more risk factors, the 5-year OS was 70% after the same treatment. These findings suggested that 3 cycles of CHOP was adequate only for patients with early stage diffuse large cell lymphoma without any IPI risk factors.

The Eastern Cooperative Oncology Group (ECOG) conducted a prospective randomized trial in a less favorable group of patients with early-stage disease. In this study, all stage I patients had bulky or extranodal disease, and patients with bulky stage II disease were included. Three hundred and fifty two patients were entered onto the trial with 2/3rd of patients having stage II disease and 1/3rd having bulky disease at presentation. Patients received 8 cycles of CHOP CTh. Sixty-one percent (215/352) patients achieved a CR. These patients were then randomized to receive RT vs. no further treatment. Patients with partial response or progressive disease were excluded from the study and received 40Gy of IFRT to the site(s) of pretreatment involvement and contiguous uninvolved region(s). In patients randomized after complete remission, the 5-year disease-free survival (73% vs. 58%; P = .03), freedom from recurrence (73% vs. 58%; P = .04), and survival (84% vs. 70%; P = .06) all favored the patients who received adjuvant involved-field irradiation. At 10 years, the disease-free survival continued to favor the addition

of RT (57% vs. 46%; P = .04), but the survival differences no longer remained statistically significant. In the CTh+RT arm 17.6% (3/17 relapses) were at the initial site of disease, whereas in the CTh arm 48.3% (15/31 relapses) occurred at the initial sites. Among patients with partial response who received 40Gy of IFRT, the 6 year FFS was 63% and OS was 69%. These results were comparable to patients who received chemotherapy alone after achieving a CR.

The GELA group compared CTh alone vs. CTh+IFRT in two separate randomized trials for age groups above and below 60 years. In the LNH93-1 study for patients less than 60 years of age, 647 patients were randomized to receive 3 cycles of inductive ACVBP + consolidation chemotherapy versus CHOP x 3 followed by 30-40Gy IFRT. At a median follow-up of 7.7 years, patients in the CTh alone arm had a significantly higher 5 year EFS (82% vs 74%, p=0.004) and OS (90% vs 81%, p=0.001). An important observation from the radiation point of view was that 41% of the relapses in the aggressive CTh only arm were exclusively in the original site and 23% in the CTh+RT arm, thus suggesting the efficacy of IFRT even with aggressive CTh for early stage disease.

The LNH93-4 study for patients above 60 years of age, 576 patients with localized lymphoma without any IPI risk factors were randomized to receive 4 cycles of CHOP alone versus 4 cycles of CHOP+40Gy of IFRT. Based on intention to treat analysis, after a median follow-up of 6.8 years, the 5 year EFS (68% vs 66%, p=0.70) and OS (72% vs 68%, p=0.20) was not significantly different between the two arms. This could be possibly be explained by the fact that none of the patients included in the study had any of the IPI risk factors.

Currently there is no ongoing study comparing R-CHOP/ CHOP like regimen versus R-CHOP/ CHOP like regimen+IFRT. Based on current evidence CTh+IFRT is considered the standard of care for early stage DLBCL although the optimal number of cycles of CTh still remains an area for research.

Suggested Reading:

1. Shenkier TN, Voss N, Fairey R, et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency. J Clin Oncol 2002;20:197-204.
2. Wilder RB, Rodriguez MA, Tucker SL, et al. Radiation therapy after a partial response to CHOP chemotherapy for aggressive lymphomas. Int J Radiat Oncol Biol Phys 2001;50:743-749.
3. Wilder RB, Tucker SL, Ha CS, et al. Dose-response analysis for radiotherapy delivered to patients with intermediate-grade and large-cell immunoblastic lymphomas that have completely responded to CHOP-based induction chemotherapy. Int J Radiat Oncol Biol Phys 2001;49:17-22.
4. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Role of Radiation Therapy in Extra-nodal Non-Hodgkin's Lymphoma

Objectives:

Primary extranodal lymphomas are a heterogeneous group of diseases of diverse etiology, pathogenesis, presentation and outcome. Before the advent of radical chemotherapy, radiation therapy (RT) was the only curative treatment for these patients. Over the recent years, the arrival of more effective chemotherapeutic agents has resulted in an increased emphasis on chemotherapy alone with less attention to the role of RT. Many a times RT is neglected in treatment protocols and trials for even localized and potentially curable presentations. There is hence a need to redefine the role of RT and review recent literature for extanodal lymphomas.

The reader of this chapter will become familiar with:

- principles of the management of aggressive extra-nodal non-Hodgkin's lymphoma with the emphasis on the role of radiation therapy.

- indications for radiation therapy in the management of these lymphomas.
- defining radiation target volume
- selecting radiation prescription

Extranodal Lymphomas (ENL) account for about 30-40% of all patients with non-Hodgkin's Lymphoma (NHL) and approximately half of those with stage I and II NHL. The most common sites of involvement are the Gastrointestinal (GI) tract (30-35% of all ENL), the head and neck region (including Waldeyer's ring and other head and neck sites), and skin, with a variety of miscellaneous sites accounting for the rest. The current consensus for primary extranodal lymphomas is that patients with stage I and II disease are generally managed with combined chemotherapy and radiation therapy (RT). Patients with stage III and IV disease and those with recurrent disease are generally managed with chemotherapy, with RT reserved for sites of initial bulky disease, or incomplete response. Radiation therapy offers the opportunity to secure local disease control while preserving organ function (for sites such as Stomach, CNS), and is frequently successfully used in patients with chemo refractory disease, recurrent disease, and in the setting of salvage chemotherapy and stem cell transplantation.

Gastric Diffuse Large Cell Lymphoma

The GI tract is the most common extranodal site for NHL and the Stomach accounts for 60% of all GI NHLs (intestinal NHL: 30% of cases, esophageal and duodenal NHL: < 10% of cases). About 60% are diffuse large cell and about 30% are MALT (associated with H. pylori) lymphomas. DLBCL of the stomach is an aggressive

lymphoma that might arise de novo or from MALT lymphoma transformation.

Historically, surgery has played a major role in the management of gastric lymphomas. Standard treatment was often a complete surgical resection followed by postoperative RT, or chemotherapy. For patients where a partial or total gastrectomy had been done, many institutes would still recommend postoperative RT, or chemotherapy. In such cases, if a microscopically complete resection had been achieved, and a full course of chemotherapy completed, further RT would not be indicated. However, any gross residual or microscopic disease is associated with a poorer prognosis and the addition of RT should be strongly considered. For favorable patients with stage IA and IIA gastric lymphoma undergoing complete resection and low dose RT (20 – 25 Gy), 10- year relapse-free survival is approximately 85%. Surgical resection is associated with a significant morbidity and a small risk of mortality, hence, non-surgical management using primary chemotherapy followed by RT is now recommended. Although there are no randomized trials, non-randomized comparisons of surgical and non-surgical approaches that adjusted for prognostic factors have found equivalent results, and the latter is generally preferred. Five year overall and disease-free survival rates for stage I/II disease typically exceed 85%.

In recent years, the treatment of choice for DLBCL irrespective of anatomic site of the lesion is rituximab plus anthracycline-based combination chemotherapy (CHOP, CEOP regimen). Although the impact of the addition of rituximab to chemotherapy regimens has not been tested in large clinical trials in patients with primary extranodal DLBCL of the Stomach, treatment must

include rituximab due to its proven therapeutic benefit in DLBCL. Similarly, consolidation with RT is indicated in these patients as there is no reason to treat limited disease gastric DLBCL differently to an analogous stage I/II nodal or extranodal diffuse large B-cell lymphoma considering that these malignancies share the same phenotypic, genetic and biological characteristics. Furthermore, many retrospective and non-randomised prospective studies have showed a lower local relapse rate for patients treated with adjuvant RT compared with patients treated with chemotherapy alone. A number of patients will also have a component of MALT lymphoma as a co-existing or precursor lesion. Patients with evidence of H. pylori infection should receive antibiotics to eradicate this infection. With optimal systemic therapy, complete response rates are very high and few early reports suggest that chemotherapy alone may be adequate for some patients, although the data are not sufficient to demonstrate that RT can be safely omitted. Until such data is available, and since the majority of gastric lymphomas are bulky, combined modality therapy remains the standard approach.

Recommendation:

Combined modality therapy with CHOP-R chemotherapy followed by involved field RT is currently the standard treatment for DLBCL of the Stomach (Level II, Grade B).

RT Dose: 35 - 40 Gy (complete response to chemotherapy)

40 - 45 Gy (partial response).

RT to be delivered at low dose per fraction: 1.5 - 1.8 Gy / fraction

RT Volume and technique:

The entire Stomach (or stomach / tumor bed in the post-operative setting), and surrounding peri-gastic and celiac lymphnode regions are to be included in the RT volume (all involved nodal regions to be included). The toxicity of RT can be reduced by using 3D conformal or intensity modulated techniques and minimizing the radiation dose to the kidneys (in particular the left kidney) and the liver. The treatment plan should be individualized for each patient according to the anatomic relationships of the stomach and also take account of organ motion due to respiration / distension.

DLBCL of the Waldeyer's Ring

Within the head and neck region, Waldeyer's Ring (WR) has been reported to be the commonest site of involvement accounting for 5–16% of all ENL and 60–70% of all ENL of the head–neck region. Majority of WR lymphomas are DLBCLs.

Historically, RT alone was considered the mainstay of treatment for stage I/II NHL of WR resulting in 5-year survival of 40–50%. However, 42–46% patients even in early stages relapsed with 22–42% relapsing at extranodal sites. Less than 10% patients suffered a local relapse within the RT portals in majority of series. The major cause of death in these patients was disseminated disease. In recent studies, the combination of Chemotherapy (CT) and relatively low doses of RT resulted in excellent relapse-free survival without significant adverse effects. A large randomized trial reporting results of stage I NHL of WR in 316 patients who were randomized to RT alone, CT alone and combined modality therapy. This study deserves special mention being the single largest phase III study for this

extranodal lymphoma. The 5-year Overall Survival was significantly better for patients treated with combined modality therapy as compared to chemotherapy alone or RT alone (90% vs. 58% vs. 56%, p ,0.001). When RT was used either alone or in combination with CT, only 5% of all relapses were in the WR, whereas in patients treated with CT alone it was almost 25%. Intestinal relapse formed 30–35% of all relapses in all the study arms. The authors claimed tolerable toxicities with combined modality management. Additionally, many retrospective studies have also found a benefit of combined modality treatment over chemotherapy alone. At the Tata Memorial Hospital, our experience with treatment of nasopharyngeal NHL revealed that patients treated with a combination of CT and RT had a significantly better outcome than those treated with CT alone (OS: 69% vs. 31%, p<0.0001). The CR (p<0.01), DFS (p<0.01) and OS (p=0.03) rates were significantly better for patients receiving a RT dose of >/= 45Gy. Similar improvement in response rates, disease free survival and overall survival rates was seen our series on primary DLBCL of the Tonsil.

Recommendation:

The standard therapy for early stage DLBCL involving Waldeyer's ring (nasopharynx, tonsil, base of tongue) is chemotherapy (CHOP-R) followed by involved field RT (Level I, Grade A). Abbreviated chemotherapy with 3 cycles of CHOP is adequate for selected early stage patients.

RT Dose: 40 - 45 Gy

RT to be delivered at low dose per fraction: 1.5 - 1.8 Gy / fraction

RT Volume and technique:

The standard RT technique includes the whole Waldeyer's ring, and bilateral cervical lymph nodes. The toxicity of RT can be reduced significantly by using 3D conformal or intensity modulated techniques and minimizing the radiation dose to the proximal critical structures of the Head & Neck region.

Paranasal Sinuses and Nasal Cavity Lymphoma

Sino-nasal lymphomas are the second most frequent lymphoma after lymphomas of the GI tract in Asian (especially in China and South-east Asia). Important differences in clinical features, phenotype, and prognosis are apparent between the Western and Asian populations. While in Asia lymphomas arising in the nasal cavity and paranasal sinuses are almost always of the T-cell or NK phenotype, in the Western World B-cell NHL is more common. B cell lymphomas of this region are treated with combined modality therapy, similar to DLBCLs of the Waldeyer's ring. Literature is mostly limited to retrospective studies which have documented the benefit of combined modality treatment. The MD Anderson study on 70 patients with paranasal/nasal cavity lymphoma, found that factors significantly influencing outcome were stage, IPI score and combined modality therapy. Furthermore, they documented only one case of CNS progression, suggesting that the risk of CNS involvement is low other than in cases with erosion of the base of the skull.

Extranodal NK/T cell lymphoma, nasal type (ENKL) is mostly endemic to East Asia. It predominantly occurs in the nasal or paranasal areas and less frequently in the skin. Most of the tumours show NK cell, but rarely T cell,

phenotypes. The Epstein–Barr virus (EBV) genome can be usually detected in lymphoma cells. Geographic localization of ENKL matches the endemic distribution of EBV, suggesting that EBV plays an important role in lymphomagenesis. It is a distinct entity in the WHO Classification characterized by CD56+ immunophenotype, and is also associated with angio-invasion, necrosis and epithelialtropism. Although ENKL is sensitive to radiotherapy, it shows a poorer response to chemotherapeutic agents than other lymphomas due to expression of p glycoprotein The Asian experience in the treatment of stage I and II nasal T/NK lymphoma is rather disappointing, with a response rate to doxorubicin-containing CT of less than 50%, and 5 year survival of approximately 40%. Patients initially treated with conventional chemotherapy regimens will eventually progress during chemotherapy. And radical RT is indicated in all cases. The tumor appears has a better response to radiation therapy, but a higher doses of > 45-50 Gy are required for best local control. Some authors have reported better outcomes with starting RT sooner (immediately at diagnosis, or after 1 cycle of Chemotherapy) and consolidating with further Chemotherapy after the completion of RT. However, RT alone is associated with a high risk (~ 60-70%) of distant disease recurrence. At present, RT followed by chemotherapy is regarded as the standard treatment strategy for limited stage ENKL (Level II, Grade B). For patients with a favorable response to combined modality treatment, preliminary data exists to support the use of high dose chemotherapy and stem cell transplantation as consolidation therapy

Thyroid lymphoma

Primary thyroid lymphoma (PTL) is a rare type of thyroid cancer. It accounts for 1–5% of all thyroid malignancies

and 1–2% of all extranodal lymphomas. The majority (~ 80%) of thyroid lymphomas present with stage I or II disease. Primary lymphomas of the thyroid are predominantly B-cell and are commonly associated with Hashimoto's thyroiditis. Most are diffuse large cell type, but up to 25% of lesions may be low-grade B-cell lymphomas (MALT origin). PTL is more common in women (3: 1 predominance) between the age of 50 and 80 years, with a peak incidence in the late 60s, and typically presents with a rapidly growing thyroid mass. DLBCL is the most common histologic subtype of PTL, accounting for approximately two-thirds of cases. In some patients, DLBCL may arise from preexisting MALT lymphoma.

Surgery is diagnostic and is not a definitive intervention for clinically evident thyroid lymphoma. With RT alone, studies have reported local control rates of over 75%, however, overall survival rates at 5 years range from 40% to 75%. To date, no randomized, controlled trials evaluating the efficacy of chemotherapy in PTL exist, but outcomes have been extrapolated from studies of nodal and other extranodal non-Hodgkin's lymphoma. A SEER database analysis of 1408 thyroid lymphoma cases found a significantly poor survival for patients who did not received RT. Combined modality treatment is currently the standard treatment approach for Thyroid DLBCL (Level II, Grade B).

Testicular Lymphoma

Primary non-Hodgkin's lymphoma of the testis accounts for about 9% of testicular neoplasms and 1–2% of all non-Hodgkin's lymphomas. Although a rare tumor, it is the most common testicular malignancy in men older than 50 years of age, and has a high incidence of bilateral

involvement. Diffuse large B-cell lymphoma (DLBCL) is the most common histotype.

Majority of papers in literature have reported a propensity for patients with testicular DLBCL to develop extranodal spread to the skin, subcutaneous tissue, central nervous system, lung, and Waldeyer's ring. Furthermore, these studies also suggest that a high proportion of patients with stage I–II diseases experience aggressive relapse, and patients with advanced disease have a very poor prognosis. On the contrary, a recent SEER database analysis of 768 patients with testicular DLBCL in fact reported a better overall prognosis for these patients as compared to patients with nodal DLBCL.

There are no available randomized studies to help define the standard therapy for testicular NHL. Orchiectomy followed by anthracycline-based chemotherapy has been associated with a 5-year survival of 30–75%. The most commonly used chemotherapy regimen is standard CHOP and other CHOP-like regimens such as MACOP-B. The current standard regimen is based on the IELSG trial which included 6–8 cycles of CHOP and rituximab and complete prophylaxis with intrathecal methotrexate and scrotal radiotherapy, and local RT to the involved lymphnodal sites. They found an improvement in the outcome with a 3-year OS and 3-year PFS of 87% and 84%.

In testicular DLBCL, the risk of contralateral testicular relapse is known to be high. This risk was reported to be 42% at 15 years among patients who did not receive prophylactic radiation in the IELSG study. Prophylactic radiation to the contralateral testis prevents testicular relapse and was also associated with better OS. These findings are supported by a recent SEER database analysis, which also reported a poorer outcome for

patients who did not receive radiation. Similar findings have been reported in smaller retrospective studies. Therefore, on the basis of available data, most experts recommend prophylactic testicular radiation.

Routine CNS prophylaxis is recommended in PTL patients of any stage since the high rate of CNS recurrence. The best strategy to prevent CNS relapse is still a matter of debate. The value of prophylactic intrathecal chemotherapy is controversial because CNS relapses occur more frequently in brain parenchyma than in meninges and also in patients who have received intrathecal chemotherapy. Hence, prophylactic cranial RT (WBRT) has been recommended by some authors.

Recommendation:

Limited stage primary testicular lymphoma should be managed with primary orchidectomy followed by R-CHOP chemotherapy, CNS prophylaxis (high-dose methotrexate ± intrathecal chemotherapy ± WBRT), and prophylactic scrotal radiotherapy. In patients with stage-IIE disease, irradiation of involved lymph nodes is advisable (Level II, Grade B).

RT Dose: IFRT: 35 - 40 Gy (complete response to chemotherapy)

40 - 45 Gy (partial response).

RT to be delivered at low dose per fraction: 1.5 - 1.8 Gy / fraction

Prophylactic scrotal irradiation (25–30 Gy; standard fractionation)

RT volume and technique:

The RT volume in IFRT for stage II disease should include the entire involved nodal region. For patients with para-

aortic involvement an inverted “Y” or “dog leg” field is used. Left renal hilar lymph nodes must be included in patients with left testicular presentation. The advent of CT based planning and 3D conformal techniques has made it significantly easier to treat these volumes as the dose to the kidneys and other organs at risk can be reduced and thus long term complications can be limited.

For prophylactic scrotal irradiation, the clinical target volume is the entire scrotum including the contralateral testis. This is usually a clinical plan and defined by palpation.

Malignant Lymphoma of the Bone

Primary lymphoma of bone constitutes 3% of primary bone tumors and 5% of extranodal lymphomas (or approximately 2% of all primary non-Hodgkin lymphomas). Males are affected more frequently than are females by primary lymphoma of bone, the male-to-female ratio being 1.8:1. All ages are affected, although lymphoma of bone is uncommon in childhood. Involved bones are those that normally contain red marrow. Common sites, in order of decreasing frequency, include the following: Femur, Humerus, Tibia, Spine, Pelvis, Sternum, Ribs, and Bones of the skull and face. Patients commonly present with local bone pain, soft-tissue swelling, and a mass lesion or pathological fracture. The diagnosis is established by bone biopsy and radical surgery is not required as a part of therapy. Nodal involvement is uncommon and about 75% of cases are diffuse large-cell lymphomas.

The absence of randomized or prospective clinical studies poses a treatment challenge, and management guidelines have been extrapolated from studies of nodal

and other extranodal non-Hodgkin's lymphoma. The recommended treatment is combined modality therapy (CMT) with chemotherapy and involved field radiation therapy. Some retrospective studies indicate that the results of combined modality therapy (chemotherapy and radiation therapy) are better than those from chemotherapy alone or radiation therapy alone, while other studies have not documented any statistically significant difference. The usual chemotherapy utilizes CHOP or similar Chop-like regimen. Recent studies have reported improvement in outcome with the addition of Rituximab. Majority of the data is retrospective and most institutes recommend CHOP based chemotherapy followed by RT to a dose of 40 – 45 Gy.

References:

1. Koch P, Probst A, Berdel WE, et al. Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96). J Clin Oncol 2005;23:7050–9.
2. Miller T, Dahlberg S, Cassady J, et al: Three cycles of CHOP plus radiotherapy is superior to eight cycles of CHOP alone for localized intermediate and high grade non-Hodgkin's lymphoma: a Southwest Oncology Group Study., American Society of Clinical Oncology, Journal of Clinical Oncology, 1996, pp 411
3. Laskar S, Muckaden MA, Bahl G, De S, Nair R, Gupta S, et al. Primary non-Hodgkin's lymphoma of the nasopharynx: Prognostic factors and outcome of 113 Indian patients. Leuk Lymphoma 2006;47:2132–2139.

4. Pingali SR, Gay G, Wright LJ, et al: Adult testicular lymphoma in the United States (1985-2004): Analysis of 3669 cases from the National Cancer Data Base. J Clin Oncol 26:15s, 2008 (suppl; abstr 19503)

5. Vitolo U, Zucca E, Chiappella A, et al: Rituximab CHOP with CNS and contralateral testis prophylaxis improves the outcome of primary testicular lymphoma: Final results of IELSG10 study. Ann Oncol 19:4s, 2008 (suppl; abstr 63)

6. Rathmell AJ, Gospodarowicz MK, Sutcliffe SB, et al: Localized lymphoma of bone: Prognostic factors and treatment recommendations. The Princess Margaret Hospital Lymphoma Group. BrJ Cancer 66:603-606, 1992

Management of Adult Burkitt's lymphoma

Burkitt's lymphoma (BL) was first described by Denis Burkitt in children in 1958. It is an aggressive B cell Non Hodgkins lymphoma that commonly occurs in children and young adults. In adults it comprises 1-5% of all Non Hodgkin lymphomas. Patients older than 40 years comprise of almost 59% of adult Burkitt lymphoma. It is characterised by a rapid doubling time of 24 hours and a very high mitotic index of nearly 100%. There is also a high incidence of CNS involvement at diagnosis ranging from 12- 63% in different studies, hence the rationale for using short duration of dose intense therapy along with CNS prophylaxis. Using this strategy in children has resulted in 60- 90% long term survival. The results in adults are more variable depending upon the patient population enrolled. There are also no randomised controlled trials in adults. Hence this review of management of adult patient keeping in mind the limitations of current literature.

Treatment

Principles of therapy include high doses of alkylating agents, frequent administration of chemotherapy, and

attention to CNS prophylaxis with high doses of systemic chemotherapy and intrathecal therapy. Standard doses of chemotherapy utilized for DLBCL such as CHOP are inadequate for treating Burkitt's lymphoma. Adult regimens for treating Burkitts lymphoma have been adopted from paediatric protocols. Table -1 summarises the various regimens used in adults.

The CODOX-M/IVAC regimen (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide and high dose cytarabine, along with intrathecal methotrexate and cytarabine) developed at the National Cancer Institute by Magrath and colleagues was initially published in 1996 (LOE III). This older series included patients with Burkitt-like lymphoma and did not use modern WHO classification system.The treatment of 20 adults and 21 children achieved an overall 92% 2 year event free survival rate(EFS).The median age of adults in this study was 24 years . These results were confirmed in a larger multicentric trial by the United Kingdom Lymphoma group LY 06 study(LOE II).The median age of patients in this study was 35 years (15-60yrs.) The regimen stratifies patients by risk, defining an uncommon (in adults) low-risk group(LR) of a single extra-abdominal mass or completely resected abdominal disease, and a normal LDH; all other patients are approached as high-risk disease(HR). Those with low risk received 3 cycles of modified CODOX M protocol, while the high risk group recived 4 cycles of alternating modified CODOX M / IVAC regimen. The 2 year EFS was 64.6% and overall survival (OS) was 72.8%. These cure rates are substantially less than the initial Magrath publication, but still better than historical data with standard-dose regimens. This regimen is however highly toxic in short term. WHO grade

IV neutropenia and thrombocytopenia was seen in 90-95% and 58-97% in LR and HR groups respectively. Grade III- IV mucositis seen in 42-53% in LR and HR groups respectively. It also required prolonged in patient care. Hence this regimen may be difficult to use in the elderly patients.

Another regimen used in adults is the Hyper CVAD regimen (LOE II). This was originaly used in Burkitts Leukemia.The median age of the patients was 58 years (range17-79 years).Patients received hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) alternating with courses of high dose cytarabine and methotrexate. Granulocyte colony-stimulating factor and prophylactic antibiotics were administered for all eight planned courses was given. CNS prophylaxis with alternated intrathecal methotrexate and cytarabine on days 2 and 7 of each course. The estimated three year survival was 49% (± 11%), it was 77% for those younger than 60 years and 17% for those older than 60 years. The worse outcome of older patients could be a result of a biologically different disease with or without its association with t(14;18), or lower treatment intensity and worse tolerance of intensive chemotherapy. Such patients received by design lower ara-C doses (1 g/m2 instead of 3 g/m2) because of a high incidence of systemic toxicity and neurotoxicity with high-dose ara-C . Grade III –IV hematologic toxicity was universal in all patients.

Several other regimens have also been used in adults with Burkitt lymphoma . Hoelzer and colleagues (LOE II) published results of 68 patients with L3 ALL (Burkitt's lymphoma) treated on 3 successive protocols,using 6 cycles of 5 day short intensive proyocol, demonstrating a leukemia-free survival rate of 71% in the most recent

regimen, with a median age of enrolled patients of 36 years. Paediatric protocols such as the LMB-89 and BFM-90 have also been used in adults yielding 5-year overall survival of upto 65%.

Chemoimmunotherapy using anti CD 20 monoclonal antibody rituximab has been used in a phase II study with Hyper CVAD.(LOE II). The median age of the patients was 46 years (range 17-77yrs.).Three year survival in this group was 89%, 90% in those less than 60 yrs and 89% in those greater than 60 yrs compared with 53%, 70% and 19% in the updated analysis of Hyper CVAD alone. Grade III-IV myelosuppression was universal. Induction mortality was 31% in those older than 60%. The improved outcome with the use of rituximab was due to the high expression of CD 20 in Burkitt lymphoma. In vitro, rituximab also sensitized NHL B-cell lines to chemotherapeutic drugs via selective down-regulation of antiapoptotic proteins Bcl-2 and Bcl-xL. Bcl-xL protects cells from drug cytotoxicity, conferring a multidrugresistant phenotype. Down-regulation of Bcl-xL by rituximab could modulate this effect and confer synergy.

Hoelzer et al. have also reported preliminary results of a chemoimmunotherapy regimen for BL or B-ALL in the elderly. Twenty-six patients aged 55 years received chemotherapy plus rituximab (375 mg/m2 i.v. Day 1 of Cycles 1-6, then 2 single doses) by Protocol B-NHL 2002. Outcome was compared with an historical cohort of 45 patients treated with similar chemotherapywithout rituximab (Protocol B-NHL90). The CR rate improved from 71% to 81%; survival rates were better with rituximab although follow-up was short (estimated 18-mo survival rate 84% vs. 6-yr survival rate 39%; p =.03). Hence both these trials show improved benefit

when Rituximab is combined with chemotherapy. It may however be omitted from the first cycle to avoid tumor lysis. (LOE III).

Elderly patients with Burkitt Lymphoma

Very few patients older than 60 yrs have been included in prospective clinical trials. Although Hyper CVAD with Rituximab has shown a favourable outcome , many elderly patients are unable to tolerate such intensive regimens. For elderly patients deemed too infirm for these intensive protocols, new therapeutic options are clearly required. These patients may be treated with standard CHOP chemotherapy with rituximab and intrathecal methotrexate, with a palliative intent (LOE III).

Conclusion

Outcome in adults with Burkitt's Lymphoma remains inferior to younger patients , but is improving. With the current evidence fit young adults should be treated with any of the short course intensive regimens, with the best results reported for CODOX-M/ IVAC and hyper CVAD with rituximab. Treating older patients with poor performance status remains a challenge in whom a balance must be sought between the treatment of disease and other co-morbidities. Future trials are needed for more inovative protocols especialy to treat elderly patients.

Table-1 Selected Prospective studies of Burkitt					
Citation	**Year**	**Regimen**	**n**	**Median age**	**2 year survival**
HoelzerB NHL 83	1996	Short duration/dose intensive; pediatric NHL based	24	33	49% (estimated)
Hoelzer B NHL 86	1996	Short duration/dose intensive; pediatric NHL based	35	36	51% (estimated)
Magrath	1996	CODOX-M/IVAC	54	24	89% (actual)
Mead	2002	Modified CODOX-M/IVAC	52	26.5	70% (estimated)
Lacasce	2004	Modified CODOX-M/IVAC	14	47	71% (estimated)
Thomas	1999	Hyper -CVAD	48	58	39% (estimated)
Thomas	2006	Hyper CVAD with Rituximab	31	46	89% (estimated)

Selected Abstracts

1. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen.

Magrath I, Adde M, Shad A, et al.

J Clin Oncol. 1996 Mar;14(3):925-34.

PURPOSE: We have used identical treatment protocols for adults and children with small non-cleaved-cell lymphoma (SNCL) for many years and report here the results of two successive treatment regimens in these age groups.

PATIENTS AND METHODS: Seventy-two patients (39 adults and 33 children) were treated with protocol 77-04 between 1977 and 1985. All patients, except those with resected abdominal disease, received 15 cycles of a combination of cyclophosphamide (CTX), doxorubicin (ADR), prednisone (PRED), vincristine (VCR), high-dose methotrexate (MTX), and intrathecal (IT) therapy. Forty-one patients (20 adults and 21 children) were treated with protocol 89-C-41, which has been used since 1989. High-risk patients received four alternating cycles (with a total duration of 12 to 15 weeks) of an intensified version of protocol 77-04 without PRED (CODOX-M), and a new drug combination consisting of ifosfamide, etoposide, high-dose cytarabine (ara-C), and IT MTX (IVAC). Low-risk patients received three cycles of the CODOX-M regimen. High-risk patients were randomized to either receive or not receive granulocyte-macrophage colony-stimulating factor (GM-CSF).

RESULTS: Event-free survival (EFS) in protocol 77-04 was 56% at 2 years and beyond. EFS in protocol 89-C-41 was 92% at 2 years and beyond. GM-CSF was associated with increased thrombocytopenia.

CONCLUSION: Adults and children with SNCL have a similar prognosis when treated with the same chemotherapy. EFS in high-risk patients has been markedly improved by including IVAC in protocol 89-C-41, and excellent results can be achieved with only four cycles of therapy. In protocol 89-C-41, GM-CSF was not beneficial.

2. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study.

Mead GM, Sydes MR, Walewski J, et al.

Ann Oncol. 2002 Aug;13(8):1264-74.

BACKGROUND: Burkitt's lymphoma (BL) is a rare and rapidly progressive form of B-cell non-Hodgkin's lymphoma. Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide and high-dose cytarabine (IVAC) is a highly effective alternating non-cross-resistant regimen developed by Magrath et al. (Magrath I., Adde M., Shad A. et al. J Clin Oncol 1996; 14: 925-934) at the US National Cancer Institute. The aim was to confirm these results in a larger, international, multi-centre study using International Prognostic Index-based criteria to assign prognostic groups, whilst slightly simplifying the protocol.

PATIENTS AND METHODS: A phase II study where: (i) low risk (LR) patients were treated with three cycles of modified CODOX-M; and (ii) high risk (HR) patients received treatment with four cycles of alternating modified CODOX-M and IVAC chemotherapy. Target of 60 patients, fit for protocol treatment, from 16 to 60 years of age with locally diagnosed, non-HIV-related, non-organ-transplant-related BL.

RESULTS: Results are given for 52 of 72 registered patients whose pathological eligibility was confirmed by central pathology review: 12 LR plus 40 HR. The majority of patients (n = 41) completed protocol treatment, but toxicity was severe, especially myelosuppression and mucositis. Overall, 2-year event-free survival (EFS) was 64.6% (95% CI 50.4% to 78.9%) and 2-year overall survival (OS) was 72.8% (95% CI 59.4% to 86.3%). For LR, 2-year EFS was 83.3% and OS was 81.5%. For HR, 2-year EFS was 59.5% and OS was 69.9%.

CONCLUSIONS: This study confirms high cure rates with this CODOX-M/IVAC approach.

3. Improved outcome in adult B-cell acute lymphoblastic leukemia.

Hoelzer D, Ludwig WD, Thiel E, et al.

Blood. 1996;87:495-508

A total of 68 adult patients with B-cell acute lymphoblastic leukemia (B-ALL) were treated in three consecutive adult multicenter ALL studies. The diagnosis of B-ALL was confirmed by L3 morphology and/or by surface immunoglobulin (Slg) expression with > 25% blast cell infiltration in the bone marrow (BM). They were characterized by male predominance (78%) and a median age of 34 years (15 to 65 y) with only 9% adolescents (15 to 20 y), but 28% elderly patients (50 to 65 y). The patients received either a conventional (N=9) ALL treatment regimen (ALL study 01/81) or protocols adapted from childhood B-ALL with six short, intensive 5-day cycles, alternately A and B. In study B-NHL83 (N = 24) cycle A consisted of fractionated doses of cyclophosphamide 200 mg/m2 for 5 days, intermediate-dose methotrexate (IdM) 500 mg/m2 (24 hours), in

addition to cytarabine (AraC), teniposide (VM26) and prednisone. Cycle B was similar except that AraC and VM26 were replaced by doxorubicin. Major changes in study B-NHL86 (N = 35) were replacement of cyclophosphamide by ifosphamide 800 mg/m2 for 5 days, an increase of IdM to high-dose, 1,500 mg/m2 (HdM) and the addition of vincristine. A cytoreductive pretreatment with cyclophosphamide 200 mg/m2, and prednisone 60 mg/m2, each for 5 days was recommended in study B-NHL83 for patients with high white blood cell (WBC) count (> 2,500/m2) or large tumor burden and was obligatory for all patients in study B-NHL86. Central nervous system (CNS) prophylaxis/treatment consisted of intrathecal methotrexate (MTX) therapy, later extended to the triple combination of MTX, AraC, and dexamethasone, and a CNS irradiation (24 Gy) after the second cycle. Compared with the ALL 01/81 study where all the patients died, results obtained with the pediatric protocols B-NHL83 and B-NHL86 were greatly improved. The complete remission (CR) rates increased from 44% to 63% and 74%, the probability of leukemia free survival (LFS) from 0% to 50% and 71% (P = .04), and the overall survival rates from 0% to 49% and 51% (P = .001). Toxicity, mostly hematotoxicity and mucositis, was severe but manageable. In both studies B-NHL83 and B-NHL86, almost all relapses occurred within 1 year. The time to relapse was different for BM, 92 days, and for isolated CNS and combined BM and CNS relapses, 190 days (P = .08). The overall CNS relapses changed from 50% to 57% and 17%, most probably attributable to the high-dose MTX and the triple intrathecal therapy. LFS in studies B-NHL83 and B-NHL86 was significantly influenced by the initial WBC count < or > 50,000/microL, LFS 71% versus 29% (P = .003) and hemoglobin value > or < 8 g/dL, LFS 67%

versus 27% (P = .02). Initial CNS involvement had no adverse impact on the outcome. Elderly B-ALL patients (> 50 years) also benefited from this treatment with a CR rate of 56% and a LFS of 56%. It is concluded that this short intensive therapy with six cycles is effective in adult B-ALL. HdM and fractionated higher doses of cyclophosphamide or ifosphamide seem the two major components of treatment.

4. Hyper-CVAD Program in Burkitt's-Type Adult Acute Lymphoblastic Leukemia Deborah

A. Thomas, Jorge Cortes, Susan O'Brien, et al.

J Clin Oncol 17:2461-2470.

Purpose: To evaluate response and outcome with a front-line intensive multiagent chemotherapy regimen in adults with Burkitt's-type acute lymphoblastic leukemia (B-ALL). Patients and Methods: FromSeptember 1992 to June 1997, 26 consecutive adults with newly diagnosed untreated B-ALL received hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD). Their median age was 58 years (range, 17 to 79 years), and 46% were H 60 years. Patients received Hyper-CVAD alternated with courses of highdose methotrexate and cytarabine. Granulocyte colonystimulating factor and prophylactic antibiotics were administered for all eight planned courses. CNS prophylaxis alternated intrathecal methotrexate and cytarabine on days 2 and 7 of each course. Results: Complete remission (CR) was obtained in 21 patients (81%). There were five induction deaths (19%). The median time to CR was 22 days (range, 15 to 89 days); 70% achieved CR within 4 weeks. The 3-year survival rate was 49% (6 11%); the 3-year continuous CR rate was 61% (6 11%). Twelve CR

patients (57%) were in continuous CR at a median follow-up of 31 years (range, 131 months to 6.51 years). Characteristics predicting for worse survival were age H 60 years, poor performance status, anemia, thrombocytopenia, peripheral blasts, and increased lactate dehydrogenase level. The 3-year survival rate was 77% for 14 patients younger than 60 years and 17% for 12 patients H 60 years (P F .01). Regression analysis identified olde age, anemia, and presence of peripheral blasts asnindependent factors associated with shorter survival. Patients could be stratified according to (1) no or one adverse feature, (2) two adverse features, and (3) all adverse features. The 3-year survival rates were 89%, 47%, and 0%, respectively (P F.01). Conclusion: Hyper-CVAD is effective in adult B-ALL. Identification of patients with high risk for relapse and improved methods to detect residual disease may result in risk-oriented approaches.

5. Chemoimmunotherapy with Hyper-CVAD plus Rituximab for the Treatment of Adult Burkitt and Burkitt-Type Lymphoma or Acute Lymphoblastic Leukemia Deborah

A. Thomas, Stefan Faderl, Susan O'Brien, et al.

Cancer 2006;106:1569–80.

BACKGROUND. Adult Burkitt-type lymphoma (BL) and acute lymphoblastic leukemia(B-ALL) are rare entities composing 1% to 5% of non-Hodgkin lymphomas NHL) or ALL. Prognosis of BL and B-ALL has been poor with conventional NHL or ALL regimens, but has improved with dose-intensive regimens.

METHODS. To evaluate the addition of rituximab, a CD20 monoclonal antibody, to intensive chemotherapy in adults with BL or B-ALL, 31 patients with newly diagnosed BL

or B-ALL received the hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen with rituximab. Their median age was 46 years; 29% were 60 years or older. Rituximab 375 mg/m2 was given on Days 1 and 11 of hyper-CVAD courses and on Days 1 and 8 of methotrexate and cytarabine courses.

RESULTS. Complete remission (complete response [CR]) was achieved in 24 of 28 (86%) evaluable patients; 3 had a partial response, and 1 had resistant disease. There were no induction deaths. The 3-year overall survival (OS), event-free survival, and disease-free survival rates were 89%, 80%, and 88%, respectively. Nine elderly patients achieved CR with all of them in continuous CR (except 1 death in CR from infection), with a 3-year OS rate of 89%. Multivariate analysis of current and historical (those treated with hyper-CVAD alone) groups identified age and treatment with rituximab as favorable factors.

CONCLUSIONS. The addition of rituximab to hyper-CVAD may improve outcome in adult BL or B-ALL, particularly in elderly patients.

6. Adult Burkitt's and Burkitt-like non-Hodgkin's lymphoma—outcome for patients treated with high-dose therapy and autologous stem-cell transplantation in first remission or at relapse: results from the European Group for Blood and Marrow Transplantation.

Sweetenham JW, Pearce R, Taghipour G, et al.

J Clin Oncol. 1996 Sep;14(9):2465-72.

PURPOSE: To investigate the results of treatment for adult patients with Burkitt's and Burkitt-like non-Hodgkin's

lymphoma (NHL) undergoing high-dose therapy and autologous stem-cell transplantation (ASCT), and to determine prognostic factors for this group.

PATIENTS AND METHODS: A retrospective analysis of 117 adult patients reported to the lymphoma registry of the European Group for Blood and Marrow Transplantation (EBMT) between June 1984 and November 1994. Seventy of these patients received high-dose therapy and stem-cell transplantation in first complete remission (CR). Data on all patients were reviewed, and prognostic factors were determined by univariate and multivariate analysis.

RESULTS: The actuarial overall survival (OS) rate for the entire group was 53% at 3 years. The major factor predicting for outcome after transplantation was disease status: the 3-year actuarial OS rate was 72% for patients transplanted in first CR, compared with 37% for patients in chemosensitive relapse, and 7% for chemoresistant patients. For patients transplanted in first CR, disease bulk at the time of ASCT was the only factor predictive of progression-free survival (PFS) and OS.

CONCLUSION: The results of high-dose therapy and ASCT for patients with relapsed disease, particularly chemosensitive relapse, are superior to those reported for conventional-dose salvage regimens. The results for patients transplanted in first CR require comparison with modern dose-intensive regimens.

Transplant in Aggressive Lymphomas

Non-Hodgkins lymphomas (NHLs) comprise a wide spectrum of diseases from indolent lymphomas to high-grade aggressive lymphomas. Along with conventional chemotherapy, high-dose chemotherapy followed by stem cell transplantation is an evolving modality of treatment that offers a long-term curative option in the treatment of NHLs. However, the optimal role and indications of this approach are still being refined; especially since the introduction of monoclonal antibodies and immunoconjugates.

Diffuse Large B-cell lymphomas

The treatment of Diffuse Large B-Cell Lymphomas (DLBCL) has been revolutionized with the introduction of the monoclonal antibody, Rituximab. Present day treatment is based on division into prognostic groups according to the age-adjusted International Prognostic Index (aaIPI) which has shown correlation with treatment and long-term responses in multiple trials. While patients in the favourable group (aaIPI 0) have response rates of around 90 % with standard R-CHOP, the patients with intermediate-risk (aaIPI 1) and high-risk (aaIPI 2-3) have

response rates of around 50-60 % and survival rates of around 60% and 40 % respectively at 4 years with R-CHOP in most of the studies. Intensification with high-dose chemotherapy followed by autologous SCT is an attractive option of increasing the response rates in this subset with high-risk and intermediate-risk disease. Patients with relapsed and refractory disease may also potentially benefit from such an approach.

i) First-line treatment of high-risk DLBCL with autologous stem cell transplant

Multiple trials have evaluated the use of autologous stem cell transplant (auto-SCT) in high-risk patients who achieve complete remission (CR) after induction chemotherapy. The results are difficult to interpret in view of differing populations and chemotherapy regimens used.

Nademanee et al did a pilot study of high-dose chemotherapy (HDCT) followed by auto-SCT in 20 patients of aggressive lymphomas of different subtypes with elevated LDH and any of the following features – bulky disease, stage III and IV, extranodal disease or with normal LDH and all the above . The event-free survival (EFS) for the overall cohort was 84 % at 34 months. The authors concluded that auto-SCT as a consolidation therapy was safe and well-tolerated.

The LNH 87-2 trial randomized 236 patients of high-intermediate and high-risk groups who achieved CR following induction therapy to further consolidation (111 patients) versus auto-SCT (125 patients) [4]. After a median follow-up of 8 years, the auto-SCT group had significantly better disease-free survival (DFS) (55% vs 39%) and overall survival (OS) (64% vs 49%).

The Milan group conducted a randomized trial for patients with aggressive lymphomas and poor-risk features. They showed a longer failure-free survival (FFS) after high-dose chemotherapy and autologous stem-cell therapy compared to a five-drug regimen. In another study, Miliped et al randomized 197 intermediate-risk patients less than 60 years with no more than 2 risk factors to CHOP chemotherapy or HDCT-auto-SCT. They found better event-free survival (56±7% vs. 28±6%) and overall survival (74±6 % vs. 44±7%) with the transplant approach as compared to the chemotherapy group in the high-intermediate risk group.

In contrast to these studies, the German High-Grade NHL Study Group conducted a randomized study comparing five cycles of CHOP-like chemotherapy against three cycles of the same chemotherapy followed by BEAM and auto-HSCT as primary therapy in 312 patients aged 60 years or younger who had aggressive NHL . OS and EFS were not significantly different between the two groups. The LNH 93-3 trial similarly did not find any difference in the survival rates among patients randomized to chemotherapy or abbreviated chemotherapy followed by auto-SCT. The criticism of these studies is the use of abbreviated chemotherapy and absence of monoclonal antibodies.

In an attempt to put all these trials in perspective, Strehl et al performed a metanalysis that included 11 randomised controlled trials (RCTs) with 2288 patients. There was statistically significant heterogeneity among the trials. Overall, mortality was comparable in the HDT/ASCT and in control arms (OR=0.97, nonsignificant). In view of the heterogeneity of trials and no survival benefit, the authors concluded that auto-SCT could not be considered as first line therapy in DLBCL.

A comprehensive Cochrane meta-analysis was later published by Greb et al. 15 RCTs including 3079 patients were eligible for this analysis. There was no statistical heterogeneity among the trials. Overall treatment-related mortality was 6% and not significantly different compared to conventional chemotherapy. Though 13 studies including 2018 patients showed higher CR rates for the HDCT arm, there was no OS benefit. The absence of benefit was seen in both low-intermediate risk and high-risk groups with the hazard ratios being non-significant, 1.41 and 0.97 respectively. There was no EFS difference observed. On sensitivity analyses, there was no association between possible factors like HDT conditioning protocols, methodology, and remission status before transplant and adherence issues. The authors concluded that despite higher CR rates, there is no benefit for HDCT in patients in CR in aggressive NHL.

Recommendation:

- Based on the available evidence, HDCT followed by auto-SCT cannot be recommended for the first-line treatment of intermediate and high-risk DLBCL in the first remission. (Level of evidence – I)

ii) Treatment of relapsed /refractory DLBCL with autologous transplantation

The seminal PARMA trial established the role of HDCT-auto SCT as the current standard of care in treatment of relapsed chemosensitive aggressive lymphoma. In this prospective randomised trial, 215 patients with relapsed lymphoma (188 patients in first relapse and 27 patients in second relapse) received 2 cycles of initial salvage chemotherapy with DHAP protocol. Of the 109 patients who achieved remission (58 % response rate), 55 were

given radiotherapy, intensive chemotherapy and autologous transplant while 54 were given four cycles of chemotherapy and radiotherapy. The median follow-up period was 63 months. The response rate was 84% after transplant and 44% after chemotherapy alone. The five-year event-free survival was 46% in the transplant group and 12% in the chemotherapy group. The overall survival rates were 53% and 32 % respectively. Subsequent analysis showed that time to relapse of less than 12 months was associated with worse results compared to relapse after 12 months.

Several studies have suggested benefit of auto-SCT in patients with refractory disease, provided they have partial or complete remission following HDCT. Such patients can be termed as having chemosensitive refractory disease. In contrast patients with chemotherapy-resistant disease do poorly with HDT, with EFS rates being less than 10%.

Recommendations

- Patients with relapsed DLBCL with relapse after 12 months and chemosensitive disease benefit from HDCT-autoSCT. (Level of evidence-I)
- Patients who relapse before 12 months can undergo transplant in the setting of clinical trials. (Level of evidence II)
- Patients with refractory and chemoresistant disease will not benefit from autotransplant. (Level of evidence II)

iii) Role of allogenic transplantation in DLBCL

Allogenic SCT offers the advantages of leukaemia-free graft and a putative graft-versus Leukaemia (GVL) effect at the cost of increased treatment related mortality (TRM).

The EBMTR group published a retrospective analysis of allogenic transplants done as the first transplant procedure for NHL over a 16-year period. There were 255 patients of high-grade NHL included in the analysis. Actuarial 4-year survival was 41.3%. Compared to a matched-pair group of autologous transplant patients, there were fewer relapses at 4 years in the allo-SCT group. However, in view of considerably higher transplant-related mortality, the overall actuarial survival was higher in the autologous transplant group. The authors concluded that allogenic transplant as first transplant procedure is associated with lower relapse rate but may not result in increased overall survival.

In an attempt to reduce the TRM, reduced intensity conditioning (RIC) protocols have been used that rely more on highly immunosuppressive regimens rather than myeloablation. RIC with fludarabine-based conditioning was used as a salvage therapy in 20 chemosensitive or stable cases in one study. There was only one case of GVHD, one death at 10 months (due to fungal infection) and one disease progression. With a median follow-up of 25 months, the estimated 3 yr survival in this pilot study was 95%. Other studies have subsequently shown OS rates of 40-50% at 3-4 years.

Rodriguez et al performed a retrospective analysis of 88 patients undergoing SCT with conventional myeloablative regimens (CMR) (48 patients) and reduced intensity regimen (RIR) with fludarabine and melphalan (40 patients). The relapse rate was significantly lower in the patients receiving CMR than in those receiving RIC (13% vs 28%). There was no difference in the TRM, 2 year PFS and OS between the two groups. The authors concluded that although RIC was a feasible alternative, it was associated with higher relapse rate, especially in

patients who had failed previous auto-SCT.

Freytes et al analysed 114 patients in the IBMTR registry who underwent allogenic transplant following post-autologous transplant relapse. Disease progression at 3 years was 52%, while treatment-related mortality was 22%. Three-year probabilities of OS and PFS were 33% and 25%, respectively. However, nearly all patients experienced disease progression on prolonged follow-up and 5-year probabilities were 24% and 5%, respectively. The authors concluded that alloSCT is usually non-curative but may benefit some patients. Most likely to benefit are patients in complete remission and good performance.

Recommendation:

- Allogenic transplant remains an option for those who have failed prior auto-SCT. Both conventional and reduced-intensity regimens may be used. (Level of evidence III)

MANTLE CELL LYMPHOMA

Mantle cell lymphoma is a distinct subtype of aggressive B-cell lymphoma. It typically affects older males and usually presents with stage IV disease. Though treatment with different chemotherapy protocols like R-CHOP and R-hyper CVAD is associated with high initial response rates, the disease usually relapses and survival ranges from 3-4 yrs in most studies. Moreover, none of the regimens show a clear plateau on follow-up that could indicate long-term cure.

i) Autologous transplantation in first remission

Multiple phase-II studies have shown the efficacy of high-dose chemotherapy followed by auto-SCT in patients who achieve a complete remission. The initial regimens used

are usually CHOP-like regimens and Hyper-CVAD with or without additional intensification with methotrexate and cytarabine.

The European MCL network conducted a trial for patients in remission after a CHOP-like regimen, randomized to consolidation with either myeloablative radiochemotherapy followed by SCT or interferon maintenance. 62 patients underwent ASCT while 60 were randomized to interferon maintenance. Patients in the ASCT arm enjoyed a significantly greater progression-free survival of 39 months as compared to 17 months in patients in the interferon arm. There was no difference in the overall survival between the two arms. The status of the disease prior to transplant contributed to the outcome with the PFS being 46 months in patients in CR as against 33 months in patients in PR. Though there was no OS benefit, the authors concluded that ASCT was a viable option in MCL.

A recent study by the CALGB has focused on the role of adding immunotherapy to intensive induction therapy followed by auto-SCT in treatment of newly diagnosed MCL patients' up to 69 years old. 78 patients received Rituximab and augmented CHOP followed by intensification with methotrexate-containing regimen and consolidation with ASCT and 2 doses of rituximab. The 5-year FFS was 56 % and the OS 64%. The regimen was safe and well-tolerated. Comparable results have been found in other studies.

Efforts to further improve the outcomes include Rituximab purging of the stem cells, radioimmunotherapy and Rituximab maintenance. In one phase 2 study, Mangel et al treated 20 patients with auto-SCT followed by 4 doses of Rituximab and found a progression-free survival of 89% at 3 years.

ii) Allogenic transplantation

Allogenic transplant remains the most curative option in MCL. Kasamon et al studied 58 patients of MCL of whom 39 underwent auto-SCT and 19 allogenic SCT. The overall 3-year PFS in this study was 51%. Recent improvement has been seen with the use of reduced intensity conditioning protocols. In one such study, Tam et al studied nonmyeloablative allogenic stem cell transplantation in patients beyond their first remission. 35 patients underwent RIC with fludarabine-based protocols. The 6-year actuarial PFS was 47 % and the actuarial OS was 53%. Importantly, both the PFS and OS had plateaus which suggested a long-term cure. Thus, RIC is an attractive emerging therapy in the subset of relapsed and refractory MCL.

Recommendations:

- Auto-SCT can be considered as standard of care in patients who achieve complete remission after R-CHOP-like induction regimens as upfront treatment. (Level of evidence I)
- Rituximab may be incorporated in maintenance and conditioning protocols as part of investigational therapy. (Level of evidence III)
- Allogenic transplant is currently the most curative option in MCL and is the standard curative option in young patients if an HLA matched donor is available inrelapsed and refractory patients. (Level of evidence II)

Suggested Reading

1. Haioun C, Lepage E, Gisselbrecht C, et al: Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: Final analysis of the

prospective LNH87-2 protocol—A Groupe d'Etude des Lymphomes de l'Adulte Study. J Clin Oncol 2000;18: 3025-3030.

2. Kaiser U, Uebelacker I, Abel U, et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for ''aggressive'' lymphoma. J Clin Oncol 2002;20: 4413–9.
3. Greb A, Bohlius J, Trelle S, et al: High-dose chemotherapy with autologous stem cell support in first-line treatment of aggressive non-Hodgkin lymphoma: Results of a comprehensive meta-analysis. Cancer Treat Rev 2007; 33: 338-346.
4. Philip T, Guglielmi C, Hagenbeek A, et al: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-5.
5. AJ Peniket, MC Ruiz de Elvira, G Taghipour, C Cordonnier. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation; Bone Marrow Transplantation 2003; 31, 667–78.
6. Kasamon YL, Jones RJ, Diehl LF, et al: Outcomes of autologous and allogeneic blood or marrow transplantation for mantle cell lymphoma. Biol Blood Marrow Transplant 11:39-46, 2005

Selected Abstracts

1. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol—a groupe d'Etude des lymphomes de l'Adulte study.

Haioun C, Lepage E, Gisselbrecht C, et al.

J Clin Oncol. 2000 Aug; 18(16):3025-30

PURPOSE: To present the final analysis, with a median follow-up of 8 years, of the LNH87-2 randomized study, which compares consolidative sequential chemotherapy (ifosfamide plus etoposide, asparaginase, and cytarabine) with high-dose therapy (HDT) using cyclophosphamide, carmustine, and etoposide (CBV regimen) followed by stem-cell transplantation in patients with aggressive non-Hodgkin's lymphoma in first complete remission after induction, focusing on high/intermediate- and high-risk patients identified by the age-adjusted international prognostic index.

PATIENTS AND METHODS: Among the 916 eligible patients, 451 presented with two (n = 318) or three (n = 133) risk factors. After reaching complete remission to induction therapy, 236 of these higher risk patients were assessable for the consolidation phase, with 125 patients in the HDT arm and 111 in the sequential chemotherapy arm.

RESULTS: Among these 451 higher risk patients, 277 (61%) achieved complete remission after induction treatment. In the population of 236 randomized patients, HDT was superior to sequential chemotherapy, with 8-year disease-free survival rates of 55% (95% confidence interval [CI], 46% to 64%) and 39% (95% CI, 30% to 48%), respectively (P =.02; relative risk, 1.56). The 8-

year survival rate was significantly superior in the HDT arm (64%; 95% CI, 55% to 73%) compared with the sequential chemotherapy arm (49%; 95% CI, 39% to 59%) (P =.04; relative risk, 1.51).

CONCLUSION: On the basis of the final analysis of this prospectively treated series of patients, retrospectively analyzed on the basis of the International Prognostic Index, we hypothesize that HDT benefits patients at higher risk who achieve complete remission after induction treatment.

2. High-dose chemotherapy with autologous stem cell support in first-line treatment of aggressive non-Hodgkin lymphoma - results of a comprehensive meta-analysis.

Greb A, Bohlius J, Trelle S, et al.

Cancer Treat Rev. 2007 Jun;33(4):338-46. Epub 2007 Apr 2.

BACKGROUND: Randomized controlled trials (RCTs) reported conflicting results on the impact of high-dose chemotherapy (HDCT) and autologous stem cell transplantation in the first-line treatment of patients with aggressive non-Hodgkin lymphoma (NHL).

METHODS: We performed a systematic meta-analysis to assess the efficacy HDCT compared to conventional chemotherapy in aggressive NHL patients with regard to complete response (CR), overall survival (OS), event-free survival (EFS), toxicity, and impact of the age-adjusted International Prognostic Index (aaIPI) risk factors. We searched the Cochrane Library, MEDLINE and other databases (1/1990 to 1/2005). Hazard ratio (HR), relative risks (RR) and 95% confidence intervals (CIs) were calculated using the fixed effect model.

RESULTS: Fifteen RCTs including 2728 patients were identified. HDCT improved CR when compared to conventional chemotherapy (RR 1.11, CI 1.04-1.18). Overall, there was no evidence for HDCT to improve OS (HR 1.05, 95% CI 0.92-1.19) or EFS (HR 0.92, 95% CI 0.80-1.05) when compared with conventional chemotherapy. However, subgroup analysis indicated OS differences (p=0.032) between good (HR 1.46, 95% CI 1.02-2.09) and poor risk (HR 0.95, 95% CI 0.81-1.11) patients. Conflicting results were reported for poor risk patients, where some studies reported improved and others reduced OS and EFS after HDCT.

CONCLUSION: There was no evidence that HDCT improved OS and EFS in good risk NHL patients. The evidence for poor risk patients is inconclusive. HDCT should not be further investigated in good risk patients with aggressive NHL but high quality studies in poor risk patients are warranted.

3. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma.

Philip T, Guglielmi C, Hagenbeek A, et al.

N Engl J Med. 1995 Dec 7;333(23):1540-5.

BACKGROUND. High-dose chemotherapy followed by autologous bone marrow transplantation is a therapeutic option for patients with chemotherapy-sensitive non-Hodgkin's lymphoma who have relapses. In this report we describe a prospective randomized study of such treatment.

METHOD. A total of 215 patients with relapses of non-Hodgkin's lymphoma were treated between July 1987

and June 1994. All patients received two courses of conventional chemotherapy. The 109 patients who had a response to chemotherapy were randomly assigned to receive four courses of chemotherapy plus radiotherapy (54 patients) or radiotherapy plus intensive chemotherapy and autologous bone marrow transplantation (55 patients).

RESULTS. The overall rate of response to conventional chemotherapy was 58 percent; among patients with relapses after chemotherapy, the response rate was 64 percent, and among those with relapses during chemotherapy, the response rate was 21 percent. There were three deaths from toxic effects among the patients in the transplantation group, and none among those in the group receiving chemotherapy without transplantation. The two groups did not differ in terms of prognostic factors. The median follow-up time was 63 months. The response rate was 84 percent after bone marrow transplantation and 44 percent after chemotherapy without transplantation. At five years, the rate of event-free survival was 46 percent in the transplantation group and 12 percent in the group receiving chemotherapy without transplantation (P = 0.001), and the rate of overall survival was 53 and 32 percent, respectively (P = 0.038).

CONCLUSIONS. As compared with conventional chemotherapy, treatment with high-dose chemotherapy and autologous bone marrow transplantation increases event-free and overall survival in patients with chemotherapy-sensitive non-Hodgkin's lymphoma in relapse.

Management of Anaplastic Large Cell Lymphoma (ALCL) in Adults

Introduction:

Anaplastic large-cell lymphoma (ALCL), is a rare disease, accounting for <5% of all cases of non-Hodgkin's lymphoma (NHL) · ALCL has a peak incidence in childhood and accounts for approximately 40% of NHL cases diagnosed in pediatric populations· ALCL occurs as two distinct clinical entities, a cutaneous and a systemic variant·

Histopathology and Immunophenotype:

On histological examination classic ALCL cell contains an eccentric nucleus which is generally horseshoe shaped or reniform with prominent nucleoli. The tumor cells are CD30 positive and also express CD25 and epithelial membrane antigen (EMA) .These cells are CD15 negative. Approximately 60% express one or more T-cell associated antigens, CD2 and CD4. One of the characteristic feature of ALCL is a translocation between chromosome 2 and chromosome 5 [t(2;5)(p23;q35)] . The translocation generates a fusion gene between nucleophosmin (*NPM*) and a receptor tyrosine kinase

gene, ALK. The NPM-ALK chimeric gene encodes a constitutively activated tyrosine kinase that is oncogenic .The ALK protein is detected in 60% to 85% of the cases using the ALK1 monoclonal antibody, showing nuclear and cytoplasmic staining in cases with the t(2;5). ALK+ cases are more common in children and have a better prognosis than ALK – cases . The cutaneous variant of ALCL is usually EMA negative . The mechanism of NPM-ALK oncogenesis is mainly mediated through the signal transducer and activator of transcription (STAT) pathway.

Risk stratification:

The single most important prognostic factor in systemic ALCL was the expression of ALK protein. In a series that included 57 patients with ALCL, the 5-year overall survival (OS) rate was 93% in patients who were ALK+ compared with 37% for those who were ALK-negative. The other risk factors include IPI score, CD 56 expression, MUC - 1 and survivin expression. In an Italian series in which ALK+ patients with a low or low–intermediate IPI score had a 5-year OS rate of 94%, whereas ALK+ patients with a high-intermediate or high IPI score had a 5-year OS rate of only 41% . In a Japanese series high IPI and CD56 positivity were independent predictors of poor outcome . Similarly newer molecular marker such as MUC-1 and survivin expression in ALCL is associated with poor prognosis.

Management of ALCL:

1. Primary Cutaneous ALCL (PCALCL):

Primary Cutaneous ALCL has indolent course, so local therapy in form of excision or local radiotherapy provides long term cure rate. There are no large series examining

the efficacy of local therapy in PCALCL. Most commonly used radiotherapy dose was 3000 cGy in 3 weeks. The response rate to radiation is in excess of 90%. Electron beam radiotherapy, which has very minimal tissue penetration, is more commonly used to minimize morbidity.

Single agent oral methotrexate in low dose is effective in PCALCL patients with widespread cutaneous disease or those in whom radiation and surgery have failed. Vonderheid et al in a series 45 patients with Ki-1+ skin lymphoma and relatively severe lymphoid pappulosis used methotrexate at median dose of 20 mg per week. Long-term disease control was achieved in 39 patients (87%) with maintenance doses given at 10 to 14-day intervals (range, 7 to 28 days). After methotrexate was discontinued, 10 patients remained free of CD30+ lesions from 24 months to more than 227 months (median, more than 127 months) .(Level of evidence: IV).

Patients with advanced disease that is refractory to local therapy and methotrexate can be treated with combination chemotherapy as used for systemic disease.

2. Systemic ALCL:

No prospective randomized study has been done in adults for management of systemic ALCL hence no standard therapeutic regimen exists for the treatment of ALCL. Most prospective trials of combination chemotherapy have been conducted in children.

Most active chemotherapeutic agents against ALCL include alkylating agents, anthracyclines, vinca alkaloids, and corticosteroids.

An Italian multicentric trial randomized 40 patients of ALCL to frontline chemotherapy with MACOP-B (methotrexate with leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) or ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). Complete response (CR) rates in both arms were in excess of 90%, with an approximately 90% chance of being relapse free at 32 month. This trial included patients of ALCL / Hodgkin disease like which are actually patients of Hodgkin's disease, which has a good prognosis with ABVD chemotherapy making the results of that trial difficult to interpret.

Fisher et al in their study which compared the standard regimen of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with three intensive chemotherapy regimens m-BACOD (methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) ; ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue); and MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) for advanced non-Hodgkin's lymphoma. They concluded that the overall survival at three years was 52 percent (50 percent in the ProMACE-CytaBOM and MACOP-B groups, 52 percent in the m-BACOD group, and 54 percent in the CHOP group; P = 0.90). There was no subgroup of patients in which survival was improved by a third-generation regimen. They finally concluded that CHOP is as efficacious as any other third generation chemotherapy regimens for treatment of patients with advanced-stage intermediate-grade or high-grade non-

Hodgkin's lymphoma. (Level of evidence: I). Due to lack of prospective study for management of ALCL and from the extrapolation of data from study by Fisher et al for advanced non-Hodgkin's lymphoma , current standard is to treat ALK + ALCL in adults with CHOP chemotherapy. Management of ALK negative is not well defined due paucicity of cases. As pre NCCN 2009, ALK negative patients are managed as per guidelines for patients for peripheral T-cell lymphoma (PTCL) with 6 to 8 cycle of multiagent chemotherapy like CHOP, EPOCH or Hyper CVAD followed by consolidation with high dose chemotherapy and stem cell rescue in all patients except with low/low- intermediate age adjusted IPI . Radiotherapy is usually given at end of treatment to initial bulky site of disease.

Role of transplantation:

Autologous Transplantation: Autologous transplant has definitive role in relapsed ALK positive ALCL. Jagasia M et al analyzed retrospective series of patients transplanted for relapsed ALCL. The 3-year OS rate was 86% in their series. ALK+ patients had an event-free survival (EFS) rate of 100% at 3 years, compared with 0% in ALK cases. (Level of evidence: IV).

In a retrospective analysis done by European Group for Blood and Marrow Transplantation (EBMT) which consisted of 64 patients with T-/null-cell ALCL of which 47% patients were in complete remission, 28% were in partial remission (PR), and 25% had more advanced or chemotherapy-refractory disease at the time of transplant. Of the 15 patients transplanted in first complete remission, only one relapsed. In contrast, 6 of 15 patients transplanted in a complete remission subsequent to the first relapse. Six of 18 patients

transplanted in PR and 14 of 16 transplanted in a refractory or relapsed disease state progressed. The actuarial OS rate at 10 years was 70%

In ALK-negative anaplastic large-cell lymphoma patients, high-dose therapy and autologous stem cell transplant does not result in long-term disease-free survival in patients even with recurrent chemotherapy-sensitive disease. (Level of evidence: III).

Allogenic transplantation: Allogenic transplant can be considered for patients with refractory or early relapsed anaplastic large cell lymphoma (ALCL) because of their poor chance of survival. BFM group retrospectively reported their data of 20 children and adolescents with high-risk relapsed or refractory ALCL who underwent allogeneic haematopoietic stem cell transplantation (HSCT). Eight patients received their transplants from matched sibling donors, eight from unrelated donors and four from haploidentical family donors. Two patients relapsed after allogeneic HSCT and died. Three patients died of transplant-related toxicity. Event-free survival at 3 years after allogeneic transplant was 75 %. There was no influence of donor type or conditioning regimen on outcome. Two of six patients with progressive disease during frontline therapy survived compared with 13/14 patients with a first relapse after frontline therapy. Two of three patients who were transplanted with active lymphoma and all five patients who received allogenic HSCT for relapse following initial autologous HSCT survived .They concluded that allogeneic HSCT is effective and has acceptable toxicity as rescue therapy for high-risk ALCL relapse and offers cure for patients refractory to chemotherapy because of a graft-versus-ALCL effect. (Level of evidence: IV)

Other therapies:

Monoclonal antibodies: CD 30 receptor over ALCL cells is emerging target for monoclonal antibodies. The chimeric anti-CD30 monoclonal antibody SGN-30 and MDX-60 a fully human anti-CD30 IgG1k monoclonal antibody , also targeting CD30 are currently in phase II trial in heavily pretreated patients with ALCL .

Role of vinblastine: French Society of Pediatric Oncology recently reported their data on single-Drug vinblastine as a salvage treatment for refractory or relapsed Anaplastic Large-Cell Lymphoma. Thirty six patients were included in this study. They were treated with vinblastine (6 mg/m2/wk) for resistant primary disease (one), a first relapse (15), or subsequent relapses (20). Fifteen patients had undergone hematopoietic stem-cell transplantation (HSCT) for a previous relapse. Six patients were not evaluable for response. Out 30 evaluable patients, 25 (83%) achieved a complete remission (CR), and five experienced progressive disease. Overall, nine of 25 patients treated with vinblastine alone have remained in CR (median, 7 years since the end of treatment), and 16 patients have relapsed. Vinblastine was still efficient for subsequent relapses. With a median follow-up of 9.2 years, 12 patients have died (four as a result of toxicity after HSCT and eight as a result of disease), and 24 patients are alive (15 following treatment with single-agent vinblastine for the last event). Five-year overall survival is 65%, and 5-year event-free survival is 30%. They concluded that Vinblastine is highly efficient in relapsed ALCL and may produce durable remissions . (Level of evidence: III).

Further trials are needed to incorporate vinblastine in management of newly diagnosed ALCL in view of its efficacy in relapsed setting.

Suggested Reading

1. Zinzani PL, Martelli M, Magagnoli M et al. Anaplastic large cell lymphoma Hodgkin's-like: a randomized trial of ABVD versus MACOP-B with and without radiation therapy. Blood 1998;92:790–794.
2. Fanin R, Ruiz de Elvira MC, Sperotto A et al. Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 1999;23:437–442.
3. Bartlett NL, Younes A, Carabasi MA et al. Phase I study of SGN-30, a chimeric monoclonal antibody (mAb), in patients with refractory or recurrent CD30+ hematologic malignancies. Blood 2002;100:362a–363a.
4. Laurence Brugie'res, Helene Pacquement et al. Single-Drug Vinblastine As Salvage Treatment for Refractory or Relapsed Anaplastic Large-Cell Lymphoma: A Report From the French Society of Pediatric Oncology. J Clin Oncol 2009 ;27:5056-5061.

Selected Absract :

Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma.

Fisher RI, Gaynor ER, Dahlberg S et al.

N Engl J Med 1993;328:1002–1006

Background: CHOP is a first-generation, combination-chemotherapy regimen that has cured approximately 30 percent of patients with advanced stages of intermediate-grade or high-grade non-Hodgkin's lymphoma in national cooperative-group trials. However, studies at single institutions have suggested that 55 to 65 percent of such patients might be cured by third-generation regimens such as m-BACOD, ProMACE-CytaBOM and MACOP-B.

Methods To make a valid comparison of these regimens, the Southwest Oncology Group and the Eastern Cooperative Oncology Group initiated a prospective, randomized phase III trial. The study end points were the response rate, time to treatment failure, overall survival, and incidence of severe or life-threatening toxicity. Dose intensity was calculated and analyzed.

Results Of the 1138 patients registered for the trial, 899 were eligible. Each treatment group contained at least 218 patients. Known prognostic factors were equally distributed among the groups. There were no significant differences among the groups in the rates of partial and complete response. At three years, 44 percent of all patients were alive without disease; there were no significant differences between the groups (41 percent in the CHOP and MACOP-B groups and 46 percent in

the m-BACOD and ProMACE-CytaBOM groups; P = 0.35). Overall survival at three years was 52 percent (50 percent in the ProMACE-CytaBOM and MACOP-B groups, 52 percent in the m-BACOD group, and 54 percent in the CHOP group; P = 0.90). There was no subgroup of patients in which survival was improved by a third-generation regimen. Fatal toxic reactions occurred in 1 percent of the CHOP group, 3 percent of the ProMACE-CytaBOM group, 5 percent of the m-BACOD group, and 6 percent of the MACOP-B group (P = 0.09).

Conclusions CHOP remains the best available treatment for patients with advanced-stage intermediate-grade or high-grade non-Hodgkin's lymphoma.

Management of Peripheral T-cell Lymphoma

Introduction

Peripheral T – Cell Lymphoma (PTCL) is a relatively rare disease. The discovery of distinct T-, B- and natural killer (NK) – cell lineages led to immunologically based classification systems. The T-cell lymphomas are grouped into “precursor” neoplasm versus “peripheral” or post thymic T-cell and NK-cell neoplasms.

Unlike mature B-cell Lymphomas, there are virtually no recurrent translocations characterizing the PTCL. The use of gene expression profiling now provide evidence for recurrent genetic changes in other PTCL subtypes. Several PTCL subtypes have viral associations that may be involved in disease pathogenesis. HTLVI was found to be etiologic agent of adult T cell leukemia & lymphoma, and Epstein- Barr Virus (EBV) was subsequently found to be associated with extra nodal NK/ T-cell Lymphoma, nasal type and angioimmunoblastic T-Cell Lymphoma. Although significant progress has been made in defining specific disease categories within the diverse group of PTCL and establishing the prognostic significance, advances in therapy have been slow. Standard

chemotherapy with CHOP has failed to be effective in T-cell lymphomas. Attention has turned to testing new chemotherapy combinations, targeted agents and high dose chemotherapy approaches specifically in PTCL.

Primary Therapy of PTCL:

CHOP like therapies have been considered standard for PTCL. With the exception of ALK-positive ALCL, the outcomes with CHOP in PTCL have been poor. Further evidence suggests that anthracyclines may not improve the outcomes in PTCL particularly PTCL – NOS.

The German NHL Group evaluated the outcome of all T-Cell Lymphomas based on treatment regimens received in seven High grade NHL studied. In the NHL – B, trial, good risk patients with T-cell lymphoma had an improved 3 year event free Survival (EFS) when etoposide was added to CHOP-14 or CHO 21. However many of these patients had ALCL. Another study evaluated a CHOP like regimen with epirubicin substituting for doxorubicin and addition of bleomycin in patients with T-Cell lymphomas, low risk disease and reported a 5 year Overall survival (OS) of 49% and a progression free survival (PFS) of 30%.

Generally treatments are similar among PTCL subtypes. However a majority of NK / T-Cell lymphoma present with localized disease and have historically receive combined modality therapy with CHOP / CHOP type chemotherapy followed by involved field radiotherapy. Often, disease progresses during the anthracycline – based therapy in patients with NK / T-Cell lymphomas suggesting inherent chemo-resistance that may be related to expression of p-glycoprotein, resulting in multidrug resistance.

Primary radiotherapy is now established as one of the key modality in the treatment of NK/TCL. This has not

been compared to combined chemotherapy alone in a randomized phase III trial.

A recent retrospective cohort study of patients treated with localized NK/T CL demonstrated that patients treated with primary radiotherapy had an equivalent 5 year OS (66% Vs 76%) and PFS (61% Vs 66%) compared to patients treated with combined modality. This study suggested no benefit for combined treatment. Additionally the study showed a response rate of 83% for radiotherapy compared to 20% after initial chemotherapy which later improved to 81% after radiotherapy. Another study compared the survival of patients who received any radiotherapy with those who did not and found improved OS in the radiotherapy group (50%) as compared to chemotherapy alone (23%). The outcome with CHOP and CHOP- like therapy has been unsatisfactory.

Beyond CHOP – New Chemotherapy combinations:

Many researches have tested intensifying chemotherapy regimens over standard – dose CHOP. In the retrospective analysis from MD Anderson Cancer Centre the comparative results of CHOP to other intensive approaches (including Hyper CVAD, ASHOP, MBACOS and MINE) suggested no significant difference in the CR rate (58% Vs 59%) or 3 year OS (43% Vs 49%). Preliminary results showed a high overall response rate of 87% with in a modified Hyper CVAD regimen using liposomal doxorubicin but similar CR, PFS and OS in comparison to their historical controls treated with CHOP.

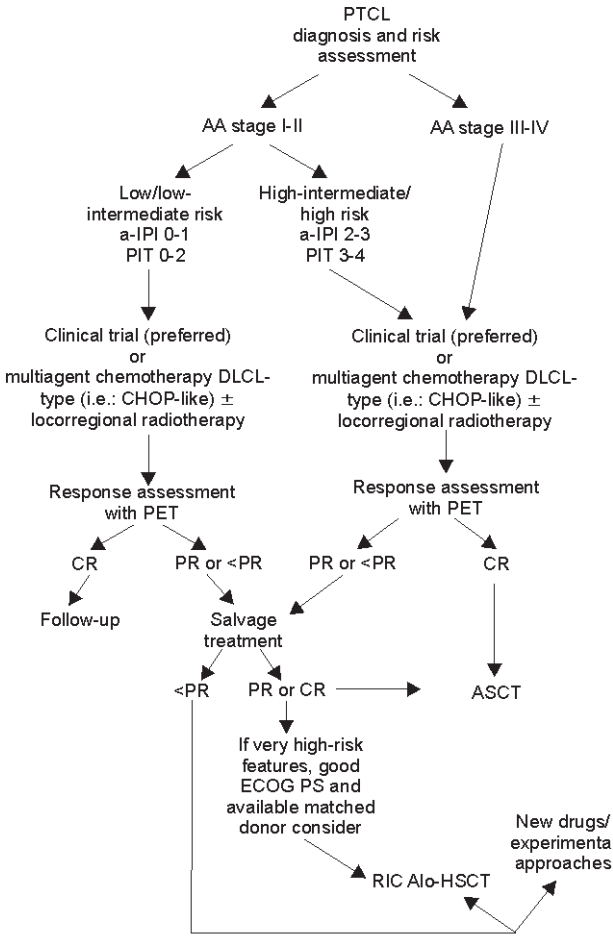
Based on high single agent activity in T-cell lymphomas, gemcitabine- based regimens have been tested in patients at relapse and in the front line therapy. Delivering an intensive regimen of CHOP –EG is feasible, but

without durable responses. The median durable remission was 7 months.

Monoclonal Antibodies in combination with CHOP:

Alemtuzumab is a monoclonal anti – CD 52 antibody that has shown activity in PTCL Modeled on the R-CHOP approach of DLBCL, alemtuzumab has been added to CHOP for PTCL. The GITIL, is a prospective Multicentre trial, combining alemtuzumab with CHOP for newly diagnosed PTCL. Patients were not required to be CD-52 positive. Patients received 8 cycles of CHOP with alemtuzumab on day – 1 of each cycle in the dose of 30 mg intravenously. The CR rate was 71% and at a median follow up of 16 months. the DFS was 54%. Immunosuppression is a concern with alemtuzumab and major infections include J-C virus activation, aspergillus's, staphylococcal sepsis and pneumonia as well as cytomegalovirus reactivation while the CR rates are impressive the OS & EFS do not appear better than historical controls with CHOP. Alemtuzumab has been added to dose adjusted EPOCH in an ongoing trial at the National Cancer Institute (NCI) for CD 52 positive PTCL. Early results suggest high response ratio but are associated with unusual opportunistic infections and grade 4 neutropenia in all patients. Bone marrow aplasia is observed at higher dose levels of alemtuzumab.

Denileukin deftitox along with bevacizumab has been used in combination therapies. As these drugs do not result in additional myelosuppression they have been easily combined with CHOP. In a phase II trial the results suggested 48% response as a single agent for denileukin in patients with relapsed PTCL. Ongoing phase II trial of



Suggested approach for treatment of Peripheral T-cell lymphoma

CHOP with denileukin deftitox for untreated PTCL showed clinical activity with response rate of 90% and little added toxicity.

Suggested Reading:

1. Schmitz N, Ziepert M, Nickelsen M et al. T-cell lymphomas in studies of the German High Grade NHL study group (DSHNHL) Ann Oncol 2008; 9 Suppl 4: 94 (abstract)
2. LI YX , Yao B, Jin J et al. Radiotherapy as primary treatment for stage IE and II E nasal Natural Killer/ T Cell Lymphoma. J Clin Oncol 2006; 24: 181 – 189.
3. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-Cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004; 15: 1467 – 1475.
4. Gressin R, Peoch M, Deconinck E et al. The VIP–ABVD regimen is not superior to CHOP–21 for the treatment of non epidermotropic peripheral T-Cell lymphoma. Final results of the LTP 95 protocol of the GOELAMS. Blood 2006; 108 Abstract # 2464
5. Escalon MP, Liu NS, Yang Y et al. Prognostic factors and treatment of patients with T-cell non Hodgkin's Lymphoma: The MD Anderson Cancer Centre experience. Cancer 2005; 103: 2091–2098.
6. Zinzani PL, Magagnoli M, Bendandi M et al. Therapy with Gemcitabine in pretreated peripheral T-Cell lymphoma patients. Ann Oncol 1998; 9: 1351 – 1353.
7. Kim JG, Sohn SK, Chac YS, et al. CHOP plus etoposide and gemcitabine (CHOP – EG) as front

line chemotherapy for patients with peripheral T Cell lymphomas. Cancer Chemotherapy Pharmacol 2006; 58 : 35 – 39.

8. Zinzani PL. Alinari L, Jani M, et al. Preliminary observations of a phase II study of reduced dose alemtuzumab treatment in patients with pretreated T-Cell Lymphoma. Hematologica 2005; 90: 702 – 703.

9. Janik JE, Dunleavy K, Pittaluga S et al. A Pilot trial of Campath – 1H and dose adjusted EPOCH in CD–52 expressing aggressive T-Cell malignancies. Blood 2005; 106 Abstract # 3348.

10. Foss FM, Sjak Shie N, Goy A et al. Phase II study of denileukin diftitox with CHOP chemotherapy in patients with newly diagnosed aggressive T-cell Lymphomas, the CONCEPT Trial: Interim analysis. Blood 2006; 108 Abstract # 2461.

Stem Cell Transplant for Aggressive T-cell Non-Hodgkin's Lymphoma

T-cell lymphomas are a rare (12% of all non-Hodgkin lymphoma) and heterogeneous group of lymphoproliferative disorders. These diseases have a geographic variation, with more nodal disease in North America and Europe, including peripheral T cell lymphomas, unspecified, anaplastic large cell lymphoma, and Angioimmunoblastic T cell lymphoma; and more extranodal disease in Asia due to Epstein-Barr virus–related nasal NK/T lymphoma and human T-cell leukemia virus (HTLV)-1–associated adult T cell leukemia/lymphoma. Although these lymphomas show a significant degree of chemosensitivity, the outcome of treatment with conventional- dose chemotherapy remains poor, with a 5-year overall survival of less than 30%. Hematopoietic stem cell transplantation (HSCT) has been explored as part of the primary therapy and also in patients with relapsed and refractory disease. Progress has been slow due to the rarity of the diseases, geographic variation, relative chemoresistance, absence of a common marker for monoclonal antibody therapy, and lack of randomized

trials. There is no consensus about optimal therapy in T/NK neoplasm, and recommendations are based on anecdotal reports, small series, and phase II trials. In this review we discuss the role of stem cell transplantation in different T-Cell Lymphomas.

Adult T-Cell Lymphoma and Leukemia (ATLL):

Because of its chemoresistance and its viral leukemogenesis, ATLL has been a unique disease for investigating therapy. The treatment of ATL has been unsatisfactory. Except for patients with the chronic or smoldering syndromes who can sometimes be followed without therapy for extended periods of time, combination chemotherapy regimens have usually been used. Although such patients may respond to the initial combination chemotherapy regimen, the OS historically has been very poor, with fewer than 10% of the patients surviving 5 years after the initiation of therapy. Improved outcomes have been reported in a Japanese study of 96 previously untreated patients with aggressive ATL treated with a complex regimen of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone). Eighty-one percent of the patients responded and the median survival time (MST) after registration was 13 months; overall survival at 2 years was estimated to be 31.3%. A variety of other new treatment approaches have been studied, including new chemotherapeutic agents, monoclonal antibodies, biologic agents, and allogeneic bone marrow transplantation.

AlloSCT was first reported as a curative option in ATLL in 1996. An analysis of 40 allo-HSCT for acute and

lymphoma types of ATLL in seven institutions in Japan between 1997 and 2002 has been reported. All evaluable cases entered complete remission (CR) after allo-HSCT and the median survival time was 9.6 months for all patients. The estimated 3-year overall and relapse-free survival, and disease relapse were 45.3%, 33.8% and 39.3%, respectively. Among 10 cases with ATLL relapse, five cases achieved CR again: three by the reduction or cessation of immunosuppressive agents, which suggested a graft-versus-ATLL (GvATLL) effect. However, univariate or multivariate analysis did not show any benefit of graft-versus-host disease (GVHD) on the prevention of relapse. Although the median survival with alloSCT (9.6 months) does not appear superior to that achieved with other therapies, the 3- year estimated overall survival of 45.3% and relapse-free survival of 33.8% suggests SCT may offer the best chance for long-term survival. These results suggested that allo-HSCT is effective for patients with aggressive ATLL, and that the GvATLL effect could be achieved even without GVHD (Level of evidence IV).

Peripheral T-Cell Lymphoma, Unspecified:

A prospective, randomized, multi-institutional trial confirmed CHOP therapy as the standard of care for aggressive lymphoma. This trial did not make any differentiation between T- or B-cell lymphomas. Therefore, CHOP therapy has remained the most common regimen for the treatment of aggressive Peripheral T-Cell Lymphoma (PTCN) though result with CHOP chemotherapy are poor in T-NHL. Because of the poorer OS in peripheral T-cell lymphoma as compared with DLBCL, bone marrow transplantation is more frequently required. Bone marrow transplantation may be as effective in peripheral T-cell lymphoma as in

DLBCL as shown by a retrospective analysis. From October, 1983, to May, 1988, 41 patients who underwent high-dose therapy and autologous hematopoietic stem cell transplant for recurrent non-Hodgkin's lymphoma were re-biopsied before transplantation to determine their immunophenotype. Seventeen of these patients were found to have a T-cell lymphoma, and 24 had a B-cell lymphoma. All patients were included in the intermediate or high grade non-Hodgkin's lymphoma categories, and none were histo-logically transformed from a low grade lymphoma. Analysis of the response to autologous transplantation in these two patient populations revealed a slightly better complete response rate for patients with T-cell lymphoma (i.e., 59% versus 42%. *P* = NS). The actuarial 2-year survival was 35% in the T-cell group compared with 30% in the B-cell group *(P* = NS). The 2-year disease-free survival was 28% for the T-cell and 17% for the B-cell patients. This result with autologous transplantation for salvage therapy revealed equivalent long-term survival and disease-free survival in both relapsed T- and B-cell non-Hodgkin's lymphoma. (Level of evidence IV)

Angioimmunoblastic T-Cell Lymphoma (AITL):

AITL typically follows an aggressive clinical course; spontaneous regression occurs on rare occasions. Treatment with Anthracycline based combination chemotherapy results in complete remission (CR) rates of 50% to 70%, but only 10% to 30% of patients are long-term survivors. Retrospective data from the European Group for Blood and Marrow Transplantation from 29 patients who received high-dose therapy followed by autologous stem cell support demonstrated AITL to be susceptible to high-dose chemotherapy with an increase in the rate of complete remission from 45%

before high-dose chemotherapy to 76% after. The probability of 5-year overall survival and event-free survival was 44% (95% CI, 22% to 66%) and 37% (95% CI, 17% to 57%), respectively. Long-term disease-free survival was observed in patients transplanted during 1st-line reatment as well as in the context of 2nd/3rd-line therapy. This evidence suggests that AITL is susceptible to high-dose chemotherapy. HDCT and autologous stem cell transplantation should be considered in selected patients with AITL. (Level of evidence IV)

Extranodal Natural Killer/T-Cell Lymphoma, Nasal &Nasal Type:

Patients with localized NK/T-cell lymphoma in the nasopharynx can be cured with a combination of chemotherapy and local radiotherapy but with disseminated disease, outlook is poor. Occasional long-term survivors are seen using the CHOP regimen. Less aggressive regimens have a uniformly poor outcome. High-dose chemotherapy and autologous bone marrow transplantation can be curative in some patients after relapse from standard therapy.

HJ Kim conducted a retrospective analysis to determine the role of high-dose chemotherapy and autologous stem cell transplantation (HDC/ASCT) in extranodal NK/T-cell lymphoma patients. In this study, they reviewed patients who had received HDC/ASCT and identified 16 eligible patients and compared the treatment outcome with historical control group (n=246). Nine patients received HDC/ASCT in the first (CR1) or second complete remission (CR2), while seven patients received HDC/ASCT as salvage. Twelve of 16 patients achieved or maintained CR after HDC/ASCT. Among the 12 patients,

five patients relapsed. Estimated 2-year overall survival (OS) and relapse-free survival (RFS) rates were 71.37 % and 25.87%, respectively. There was a tendency of better survival in patients who received HDC/ ASCT as compared to those who did not (P=0.091). In subset analysis, patients who underwent HDC/ASCT at CR (P=0.049) and patients with stage III or IV (P=0.001) had a favorable outcome. Patients with NKIPI 3, 4 or EUNKTL, who underwent HDC/ASCT, had more prolonged survival without statistical significance (P=0.055 and 0.056). Hence HDC/ASCT may be considered as a treatment option for patients with extranodal NK/T-cell lymphoma, especially those in CR, with advanced disease (stage III/IV or EUNKTL) and high NKIPI scores. A recent retrospective analysis also suggested that extranodal NK/T-cell lymphoma patients in CR with high NKIPI risk scores at diagnosis should receive full consideration for HSCT. (Level of evidence IV)

Enteropathy-associated T-Cell Lymphoma (EATL):

Besides aggressive nutritional support with parenteral or enteral and gluten-free diet (in patients celiac disease), adriamycin-based combination chemotherapy should be considered for each patient with a diagnosis of EATL. The course is aggressive, and poor response to standard chemotherapy has been reported. In a small series reported by Bishton MJ et al, role of high-dose therapy and autologous stem cell transplantation, appear promising.[12]Six patients were treated with two cycles of IVE (ifosphamide, etoposide, epirubicin), followed by two cycles of high-dose methotrexate (3 g/m2) with folinic acid rescue and a BEAM (carmustine, etoposide,

cytarabine, melphalan) autograft. Enteral feeding was given throughout treatment. Four patients remain alive in complete remission at 1.83–4.32 years; two have relapsed. Given the historically poor outcome in these patients, this regimen appears very promising in the treatment of EATL. (Level of evidence IV)

Hepatosplenic T-Cell Lymphoma (HSTCL):

CHOP or CHOP-like first-line regimens with salvage high-dose therapy with autologous transplant have been ineffective. The clinical course of HSTCL is usually aggressive despite multiagent chemotherapy. Allogeneic transplantation inducing longer remission as against autologous transplant was reported by a retrospective study. In a recent case report, a patient with HSTCL was treated with Alemtuzumab and the patient subsequently underwent unmatched, unrelated stem-cell transplantation. The patient was alive with no evidence of disease after almost 21 months of follow-up. Hence allogeneic transplant should br considered for patients with HSTCL at 1st CR. (Level of evidence IV)

Subcutaneous Panniculitis like T-Cell Lymphoma (SCPTCL):

The clinical course of SCPTCL is variable, ranging from indolent disease to rapidly fatal fulminant hemophagocytosis. When treatment is warranted, most patients respond to systemic combination chemotherapy or local radiation therapy, but the responses are usually transient. However, the long-term outlook with this disorder is poor, and early consideration of aggressive approaches, including autologous or allogeneic stem cell transplantation, is recommended based on case reports highlighted in table. (Level of evidence V)

Table I. Published cases concerning autologous and allogeneic blood stem cell transplantation for aggressive subcutaneous panniculitis-like T-cell lymphoma

Case	Age (y)/ Sex	Auto/ Allo	Previous therapy	Outcome
1. Romero et al	23/F	Auto	Steroids, CHOP, mini-BEAM	Died 6 wk post-tx
2. Haycox et al	39/M	Auto	CHOP, DHAP+RT, ICE	CR/16 mo+
3. Koizumi et al	20/M	Auto	CHOP-E	CR/12 mo+
4. Hashimoto et al	21/M	Auto	CHOP+RT, VIP-E	CR/14 mo+
5. Reimer et al	35/F	Auto	CHOP	CR/5 mo+
6. Mukai et al	24/M	Auto	CHOP	CR/24 mo+
7. Mauro Alaibac et al	32/F	Auto	VACOP-B, vinorelbine, DHAP	CR/24 mo+
8. Michiko Ichili et al	37/F	Allo	CHOP-E	CR/53m0+

Anaplastic Large Cell Lymphoma:

ALCL can be subdivided into three primary diseases (systemic ALK-positive, systemic ALK-negative, and primary cutaneous ALCL). A prognostic model and risk stratified treatment has been proposed. [25] ALK-positive ALCL has a better prognosis than systemic ALK negative ALCL. Five-year overall survival following anthracycline therapy is 60-93% for ALK-positive compared to 11-46% for ALK-negative ALCL. Treatment regimens used for anaplastic cell lymphoma of the primary systemic type are the same as those used in DLBCL, without rituximab therapy. A worse prognosis can be seen in ALK-positive patients with B symptoms, a high IPI, small cell variant

histology, and CD56 or survivin (a member of the inhibitor of apoptosis family) expression. More intensive therapy could be justified in selected ALK-positive patients with these adverse features.

Autologous stem cell transplantation (ASCT) has been studied prospectively and retrospectively in ALCL. In a retrospective series of patients transplanted for relapsed ALCL, the 3-year OS rate was 86%. ALK+ patients had an event-free survival (EFS) rate of 100% at 3 years, compared with 0% in ALK" cases. There was a very small number of patients with cutaneous ALCL, though all relapsed but followed an indolent course after ASCT. A nearly identical result was noted in a Finnish series of 14 patients undergoing ASCT for ALCL after conditioning with BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) or BCNU, cytarabine, etoposide, and melphalan (BEAM). In that report, the 5-year OS rate was 86%, and again the small number of PCALCL patients invariably relapsed. ALK staining was not performed in the Finnish trial, but the poor outcome with ASCT for ALK" ALCL was confirmed in a separate series of 15 ALK" patients. In that analysis, 13 patients relapsed after transplant and the median PFS duration was only 12 weeks, with a median OS time of 72 weeks. The European Group for Blood and Marrow Transplantation (EBMT) has reported the largest ASCT series to date. The analysis consisted of 64 patients with T-/null-cell ALCL. The median age was 25. Forty-seven percent of patients were in complete remission, 28% were in partial remission (PR), and 25% had more advanced or chemotherapy- refractory disease at the time of transplant. Eighty-one percent of the patients were conditioned with chemotherapy alone and 75% received

marrow stem cells. Of the 15 patients transplanted in first complete remission, only one relapsed. In contrast, 6 of 15 patients transplanted in a complete remission subsequent to the first relapsed. Six of 18 patients transplanted in PR and 14 of 16 transplanted in a refractory or relapsed disease state progressed. The actuarial OS rate at 10 years was 70%. Disease status at transplant, younger age, absence of B symptoms, and lack of extranodal disease indicated a better prognosis in multivariate analyses. Several studies have evaluated the efficacy of upfront ASCT for ALCL. A French series examined 15 patients with ALCL (three with B-cell markers), including seven who were ALK+, treated with chemotherapy consisting of two alternating anthracycline-containing regimens. Patients who responded then underwent BEAM conditioning followed by ASCT. All patients achieved a CR and there were no relapses. The EFS and OS rates at 5 years were both 87%. Based upon the patient's age-adjusted IPI, the EFS and OS rates would have been expected to be 71% and 69%, respectively. Although these results are excellent, the lack of a prospectively identified control group makes interpretation of the outcome difficult. Other trials of upfront ASCT have shown similarly promising results but are hampered by the same issues of selection bias and lack of a randomized control group. Clearly ASCT has a role in ALCL. The question remains whether to transplant patients upfront or to only transplant patients who have relapsed. Given the favorable prognosis of ALK+ patients, particularly those with low/low–intermediate IPI scores, it is difficult to justify upfront transplantation in that particular subgroup. More refined, molecularly based prognostication systems and homogeneous trials of true ALCL cases will hopefully allow us to better identify those

patients who may benefit from upfront ASCT. Limited data would suggest that ASCT is not effective for ALK" patients with relapsed disease, so these individuals may better be served by participating in clinical trials investigating new therapies. Whether upfront ASCT improves the outcome in ALK" patients is unclear. Several reports have described successful allogeneic stem cell transplantation for ALCL . There is no systematic literature comparing this approach with ASCT. Given the toxicity of allogeneic transplantation and the favorable outcomes obtained with conventional chemotherapy and ASCT, allogeneic transplant can only be recommended for the most refractory patients, preferably in the setting of a clinical trial. (Level of evidence III)

Suggested Readings:

1. Rudiger T, Weisenburger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplasticlarge-cell lymphoma): results from the Non- Hodgkin's Lymphoma Classification Project. Ann Oncol. 2002;13:140-149.

2. Fukushima T, Miyazaki Y, Honda S, et al. Allogeneic hematopoietic stem cell transplantation provides sustained long-term survival for patients with adult T-cell leukemia/lymphoma. *Leukemia* 2005;19:829.

3. Reiser M, Josting A, Soltani M, et al. T-cell non-Hodgkin's lymphoma in adults: clinicopathological characteristics, response to treatment and prognostic factors. Leuk Lymphoma. 2002;43:805-811.

4. Kim HJ, Bang SM, Lee J, et al. High-dose chemotherapy with autologous stem cell transplantation in extranodal NK/T-cell lymphoma:

Table 2. Selected Studies of Hematopoietic Stem Cell Transplantation in Different Subtypes of Peripheral T-Cell Lymphomas

Author	No. of Patients	Disease Status	Conditioning Regimen	Median F/U (mos)	CR Rate	OS Rate	TRM
Blystad et al	40 Mixed	Mixed	BEAM (autologous) BEAC	36	80%	58% at 3 yrs	8%
Rodriguez et al	29	Relapsed/ refractory	Various (autologous)	43	86%	39% at 3 yrs	7%
Kahl et al	10	Mixed	Various (autologous)	12	70%	58% at 1 yr	10%
Angelopoulou et al	35	Relapsed/ refractory	Various (autologous)	33	N/A	33% at 5 yrs	3%
Rodriguez et al	115	Mixed	BEAM (autologous) BEAC	37	91%	56% at 5 yrs	8%
Song et al	36	Relapsed/ refractory	Mel/VP16 ±TB(autologous)	42	N/A	48% at 3 yrs	17%
Jantunen et al	37	Mixed	Mixed BEAM (autologous)	24	81%	63% at 5 yrs 1	11%
Corradini et al	17	Relapsed/ refractory	Fludarabine, Thiotepa,, cyclophosphamide (allogeneic)	28	76%	81% at 3 yrs	6%
Reimer et al	21	First CR	BEAM (autologous)	15	100%	76% at 15 mos	0%

OS- overall survival, CR-complete response, TRM- treatment related mortality.

a retrospective comparison with non-transplantation cases. *Bone Marrow Transplant* 2006;37:8

5. Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. *Br J Haematol* 2007;136:111.

Table 3. Suggested role for stem cell transplantation (SCT) in T/NK neoplasm.

Disease Type	Timing of SCT
Anaplastic large cell, ALK-positive	Auto – after relapse
Anaplastic large cell, ALK-negative	Auto – if IPI e" 3 or e" group 3*
Angioimmunoblastic PTCL, unspecified	Auto – if IPI e" 3 or e" group 3 Auto – if IPI e" 3** or e" group 3
Nasal, localized disseminated	Auto – after relapse Auto or allo
Enteropathy associated	Auto
Subcutaneous panniculitis-like	Auto if hemophagocytosis
Hepatosplenic, γδ	Allo over auto
T prolymphocytic leukemia	Allo over auto
Adult T cell leukemia/lymphoma	Allo over auto
Aggressive NK leukemia	Allo

*4 prognostic factors in PTCL: age, performance status, LDH and bone marrow involvement (alloSCT will need to be considered in the latter). Group 3 had 2 or more factors and group 4 had 3 or 4 factors.[25]

** Because 5-year survival > 60% has been observed in PTCL/ U only with IPI d" 1, early SCT should be nvestigated in PTCL/U with IPI e" 2.

Management of Pediatric Diffuse Large Cell and Burkitt's Lymphoma(B-NHL)

Introduction

Burkitt lymphoma (BL) is a highly aggressive B-cell neoplasm characterized by the translocation and deregulation of the c-myc gene on chromosome 8. Burkitt-like lymphoma (BLL) is proposed as a morphologic variant of BL. BL comprises 30 percent of non-endemic pediatric lymphomas. Diffuse large-cell NHL (DLCL) constitutes approximately 20% of pediatric NHL. DLCL and BL have similar clinic-biological behavior, treatment and outcome in children. Henceforth these would be referred together as B-NHL in the following text.

Clinical features and Pathology:

Three distinct clinical forms of BL are recognized: endemic, sporadic, and immunodeficiency-associated. Although they are histologically identical and have similar clinical behavior, there are differences in epidemiology, clinical presentation, and genetic features, with the

endemic (African) variant found predominantly in equatorial Africa. In HIV positive patients, BL typically affects those with a relatively high CD4 count and no opportunistic infections.

The malignant cells show a mature B-cell phenotype and are negative for the enzyme terminal deoxynucleotidyl transferase (TdT). These malignant cells usually express surface immunoglobulin, most bearing surface immunoglobulin M with either kappa or lambda light chains. A variety of additional B-cell markers (e.g., CD20, CD22) are usually present, and almost all childhood Burkitt/Burkitt-like lymphoma/leukemia express CALLA (CD10). Burkitt lymphoma/leukemia expresses a characteristic chromosomal translocation, usually t(8;14) and more rarely t(8;22) or t(2;8). Each of these translocations juxtaposes the c-myc gene to immunoglobulin locus regulatory elements, resulting in the inappropriate expression of c-myc, the gene involved in cellular proliferation. Pediatric Burkitt lymphoma patients whose tumors also contain cytogenetic abnormalities of 7q, 13q, or 22q have an inferior outcome on current chemotherapy protocols. [Level of evidence: 3A]

The distinction between Burkitt and Burkitt-like lymphoma/leukemia is controversial. BL consists of uniform, small, non-cleaved cells, whereas BLL diagnosis, as per WHO guidelines, be reserved for lymphoma resembling BL with more pleomorphism, large cells, and a high proliferation fraction (i.e., Ki-67[+] of at least 99%). Cytogenetic evidence of c-*myc* rearrangement is the gold standard for diagnosis of Burkitt lymphoma. Studies have demonstrated that the vast majority of BLL have a gene expression signature similar to Burkitt lymphoma. [Level of evidence: 3A].

DLBL cell express the mature B- cell markers(e.g., CD20, CD22).

Despite the histologic differences, DLBL, Burkitt and Burkitt-like lymphoma/leukemia are clinically very aggressive and are treated together on similar protocols with very aggressive regimens. When the bone marrow is involved, the distinction between BL and leukemia is somewhat arbitrary: If more than 25% of the marrow is replaced by lymphoblasts, the patient is considered to have leukemia; if less than 25%, the patient is considered to have advanced-stage NHL with marrow involvement.

Workup

For confirmation of diagnosis, staging and therapeutic planning, following tests are required;

- Blood tests: Complete blood count, Liver function test, Renal function test, Serum electrolyte Calcium, Phosphorus, Uric acid, LDH, ESR, HIV
- Diagnostic biopsy for Histopathology/ Immunophenotype/ genetic analysis or pleural fluid/ ascitic fluid for cytological diagnosis if present.
- Bone marrow aspiration and biopsy
- CSF analysis
- Radiological tests: CT/MRI of the primary site and thorax, abdomen, and pelvis. PET-CT may be potentially useful for assessing the speed of response and confirmation of post-therapy remission (CR) but is currently not standard of care.

Staging & risk stratification:

The St. Jude's children's research hospital staging classification is used for staging which has taken in to consideration increased extra nodal involvement;

metastatic spread to the bone marrow (BM) or CNS, and noncontiguous spread of disease in this group. However with the increasingly intensive treatment protocols, the outcome difference between various stages has become insignificant. Hence, various study groups have utilized varying risk stratification systems incorporating extent of resection, degree of bone marrow & CNS involvement and LDH with variable success in their studies[-]. These have been highlighted in table 1.

Treatment

B-NHL in children is generally considered to be widely disseminated from the outset, hence, combination chemotherapy is recommended for most patients. There are two potentially life-threatening clinical situations that are often seen in children with B-NHL: (1) intestinal obstruction or perforation and (2) tumor lysis syndrome. These emergent situations should be anticipated and addressed immediately. Hyperhydration and allopurinol or rasburicase (urate oxidase) are essential components of supportive therapy in all these patients.

Principles of treatment:

B-NHLs are characterized by very high growth fractions and very short doubling times. Hence, treatment protocols involve an intensive short multi-agent chemotherapy given in courses of 3-5 days with a schedule characterized by fractionation or continuous infusion of drugs. The aim is to maintain a cytotoxic level of the drug over a period of atleast 48-72h, during which every malignant cell should have a chance to enter the cell cycle. Also, because of the rapid doubling time of tumor cells, and the potential for tumor re-growth before bone marrow recovers, the courses have to be administered with the shortest intervals in between.

Over the past 20 years the different pediatric oncology groups have incorporated above principles in the treatment of pediatric NHL. Several conclusions become evident on review of multiple cooperative group protocols (SFOP, BFM, POG and CCG) and published and preliminary results of ongoing trials.

1. More than 75% of newly diagnosed children with advanced Burkitt's with or without CNS disease are currently cured of disease.
2. Radiation and/or surgery do not play a major role in the curative therapy for this disease except in emergency situation such as surgery for intestinal obstruction.
3. The most effective regimens combine short-term (< 9 months) aggressive multiagent chemotherapy with alkylators, antimetabolites, anthracyclines and IT chemotherapy.
4. Toxicity and toxic deaths remain a significant problem with renal failure, infections and mucositis being the most common severe acute non-hematological toxicities.
5. High dose methotrexate (HD-Mtx) has been substantially established as the most efficacious drug in managing B-NHLs However, the best dosing, and the best infusion period of HD-Mtx is still ambiguous.

The important trials are summarized below;

1. SFOP

The LMB 84 (1984 – 87) study randomized 216 CNS negative patients with advanced B-Cell lymphomas and leukemias to 4 months vs. 7 months of intensive therapy.

The EFS was 78% with equivalent survival between treatment arms. Patients with B-ALL or stage IV disease had a 67% 4 year EFS. The study confirmed the previous French studies of high survival without radiotherapy or debulking.

In LMB-89 the study goals were to deliver chemotherapy stratified according to tumor burden (stage, resection status, bone marrow and CNS involvement) and response to chemotherapy. The dose of MTX was increased to 3 gm/m2 in group B patients and 8 gm/m2 in group C patients and added high dose ARA-C plus VP-16 (CYVE) to group C patients. The 5 year EFS and OS in group B patients were 94 % and 92%, respectively. Group C patients also had improved survival from previous LMB regimens with 5 year EFS and OS of 85 % and 84 %, respectively. The toxicity in this trial was also substantial.

International FAB-LMB-96 study (CCG, SFOP, UKCCSG):

In the multinational LMB-96 study, the outcome of group B patients, who had a greater than 20% response to cytoreductive prophase, was not affected by a reduction of the total dose of cyclophosphamide by 50% and elimination of one cycle of maintenance. The 3-year EFS was 98%, 90%, and 86% for stage I/II, stage III, and stage IV (CNS-negative) patients, respectively, while patients with PMBCL had a 3-year EFS of 70%. However, in high-risk group C patients, reduction of therapy resulted in inferior outcome. Patients with leukemic disease only, and no CNS disease, had a 3-year EFS of 90%, while patients with CNS disease at presentation had a 70% 3-year EFS. This study identified response to prophase reduction as the most significant prognostic factor, with

poor responders (i.e., <20% resolution of disease) having an EFS of 30%.

2. BFM

In NHL-BFM 90 trial, patients received a cytoreductive pre-phase and then were stratified into three treatment groups. R1 patients (completely resected tumors) received 2 courses of multiagent therapy with ID-MTX (500mg/m2). R2 patients (extra-abdominal primary and LDH < 500 U/L) received 4 courses of multiagent chemotherapy with HD-MTX (5 gm/m2). R3 patients (most advanced patients including CNS +) received 6 courses of therapy. Incomplete responders after two cycles of therapy received an added intensification containing high dose ara-C and VP-16. The 6 year EFS was 89% and overall survival was 100%, 96% and 78% in R1, R2, and R3 patients, respectively.

In the BFM-95 trial, it was shown that reducing the infusion time of methotrexate from 24 hours to 4 hours resulted in inferior outcome for R3 and R4 group patients. EFS with best therapy in BFM-95 was more than 95% for R1 and R2 group patients and was 93% for R3 and R4 group patients. Inferior outcome was observed for patients with CNS disease at presentation (70% 3-year EFS).

3. POG

The Pediatric Oncology Group (POG) has had a similar overall strategy of dose intensification and aggressive non-radiation CNS directed therapy in advance B-cell disease.

In POG 8617, 133 children with Murphy Stage IV small noncleaved-cell lymphoma (SNCCL) or B-ALL were treated with fractionated cyclophosphamide, doxorubicin

and vincristine followed by methotrexate (1 gm/m2) and high dose (3 gm/m2) ara-C and IT therapy. At 4 years, the estimated EFS rate was 65% and 79% in patients with B-ALL and stage IV SNCCL, respectively.

The POG 9317 study (which also included stage III patients) randomized CNS negative patients to additional therapy with VP-16 and Ifosfamide. In this trial all CNS positive patients were non-randomly assigned the VP-16/Ifos arm and achieved a two year EFS of 79% which was better than the 58% EFS for CNS positive patients on POG 8617 ($p = 0.02$)

Modified MCP-842 protocol:

To improve the outcome of childhood NHL in India, the MCP 842 Protocol, a short duration intensive chemotherapy protocol was initiated in 1987. 160 previously untreated patients < 24 years of age with B-NHL (Burkitt's lymphoma [BL]: 107 and Diffuse large B-cell NHL [DLBL]: 53) were enrolled between 1987 and 2006. Treatment consisted of eight alternating cycles of two regimens, A (Cyclophosphamide, Adriamycin, Vincristine and Cytosine-arabinoside) and B (Etoposide, Vincristine, Methotrexate, and Ifosfamide). Intrathecal methotrexate and cytosine arabinoside were administered in the first 4 cycles. No radiotherapy or high dose methotrexate was given. The protocol was modified in 2003 with addition of COP prophase, low-dose rasburicase in patients with clinical tumor lysis syndrome and optimization of dose intensity with granulocyte colony stimulating factors.

Recent analysis has shown that 10 year EFS analyzed stage wise is 76% and 73% for localized stages (I & II) and advanced stages (III & IV) respectively with an overall EFS of 74% and OS of 82.7%. The EFS has improved

from 68% to 86% and relapse rate decreased from 17% to 3% after modification of protocol in 2003 ($P < 0.05$). The toxic death rate in this study is less than 5%. The average cost of protocol is $4000 (Rs 2 lakhs) for the entire therapy.

The current standard of treatment for pediatric Burkitt's lymphoma can be summarized as below:

Treatment of limited stage disease (table-2)

As seen above, children with limited stage B-cell NHL (St. Jude stage I and II, CCG limited stage, BFM R1 or FAB group A) have a superb prognosis with an estimated five-year EFS of 90-95% with minimal chemotherapy (range 6 weeks to 6 months). There are several multiagent chemotherapy regimens that have resulted in this excellent outcome, including COPAD (6weeks; FAB), COMP (3-6months; CCG and POG), MCP-842(6-8cycles-4months)or cyclophosphamide and prednisone followed by dexamethasone/ifosfamide/Ara-C/VP-16/ methotrexate and dexamethasone/ cyclophosphamide/ methotrexate/doxorubicin (12 weeks; BFM).

All completely resected stage I and abdominal stage II (group A) are treated with two cycles of multiagent chemotherapy and without intrathecal chemotherapy (FAB-LMB-96)(Level of Evidence 2A). For unresected stage I/II disease (group B), reduced duration therapy of four cycles of chemotherapy following a cytoreduction phase and reduced cumulative doses of cyclophosphamide and doxorubicin can be used as per FAB-LMB-96 (Level of Evidence 1A).

Treatment of advanced stage disease(table-2)

Patients with disseminated BL have an 80% to 90% long-term survival. As per the BFM -90, all patients receive a

cytoreductive prophase, which is followed by four cycles of intensive chemotherapy for R2 group; R3 patients receive five cycles of intensive chemotherapy; and R4 patients receive six cycles of intensive chemotherapy (Level of Evidence 1A).[9]

The standard treatment guidelines based on BFM-95 and LMB-90 protocols have been highlighted in tables 4-6. MCP-842 (8cycles-6 months) can also be used especially in centres with no facilities for methotrexate levels and inadequate infrastructure with excellent outcomes.

CNS directed therapy

Intensive CNS directed therapy with preventive and curative intent is necessary. HD-Mtx and HD Ara-C besides their clear systemic effect are essential because of their passage into CNS.[9] It is now admitted that cranial irradiation is not necessary even if there is CNS +ve disease (Level of Evidence 1A).[10] This has been supported by studies from both the BFM and FAB/LMB groups. Intensive intrathecal therapy is however required, though it is still unclear whether intraventricular therapy is superior to intrathecal, more so because insertion of an Omaya reservoir may not be feasible everywhere.

Treatment of relapse

The outcome of relapsed patients with BL is dismal because most relapses tend to occur early during active chemotherapy, and drug resistance is a major obstacle to successful salvage. Multiagent salvage regimens that have been studied include DHAP (dexamethasone, high-dose cytarabine, and platinum), VIPA (etoposide, ifosfamide, and high-dose cytarabine), ICE (ifosfamide, carboplatin, and etoposide) and MIED (high-dose methotrexate, ifosfamide, etoposide, and dexamethasone). Rituximab have been reported to be

active in the relapse setting. Current investigational protocols combine chemotherapy with rituximab followed by allogeneic or autologous SCT. The outcome is more favorable for patients who achieve a second remission before proceeding to SCT.

Emerging strategies

Role of Rituximab (Anti CD 20)

Rituximab is a mouse/human chimeric monoclonal antibody targeting the CD20 antigen. Among the lymphomas in children, both DLBCL and BL express high levels of CD20. Adult clinical trials have demonstrated that rituximab is mainly active against bcl-6–negative DLBCL patients. Rituximab has been safely combined with standard CHOP chemotherapy and an intensive chemotherapy regimen for BL. There are an increasing number of case reports describing complete responses to rituximab in relapsed B-cell lymphoma/ leukemia in children but most children with B-NHL, in particular BL and DLBCL, are bcl-6 positive and hence its precise place in current strategies remains unclear. A recently published COG report submits a 60% response rate in children with recurrent DLBCL, BL, and B-ALL using Rituximab with ICE. The COG is currently exploring the use of rituximab in combination with the intensive chemotherapy regimen in the most recent multinational cooperative study, and in combination with cyclophosphamide and prednisone for patients with post-transplant lymphoproliferative disease. The initial data suggests that Rituximab with intensive chemotherapy is safe and feasible with equivalent outcome.

Minimum residual disease detection

While therapeutic strategies in treating pediatric NHL have markedly improved, the challenges in identifying

residual disease still remain. Detecting minimal residual disease (MRD) could be used as a tool in monitoring therapeutic efficacy and/or assessment of early relapse. Detecting residual disease and recurrent disease are two separate entities but the possibility of designing and using unique patient-specific primers (PSPs) to detect disease can potentially be applied to both clinical scenarios. Polymerase chain reaction (PCR)-based techniques have been utilized to assess MRD in adult and pediatric patients with leukemia and subsets of lymphomas. Similarly, in BL, a long-distance polymerase chain reaction (LD-PCR) assay that can detect the t(8;14) has been used to test minimal disseminated disease (MDD) at diagnosis and during therapy and has been found superior to BM aspirate & BM biopsy in the assessment of MDD and to determine its response kinetics in BL. However, t(8;14) is detectable in only about 70% of patients, thus preventing MRD studies by this approach in the remaining patients. A recent study has suggested that the combination of LD-PCR and Ig-based assays might be more successful in MRD analysis.

Conclusion

Burkitt lymphoma is a potentially curable malignancy in majority of cases. Although some questions remain, general guidelines of the initial treatment are now well established. The remaining therapeutic challenges concern relapses, maintaining cure with minimal treatment related toxicities, and role of monoclonal antibody, MRD and PET-scan in front line treatment.

Table 2 Treatment protocol recommendations

Stage of disease		Treatment protocol		EFS
Localised Disease	Completely Resected	NHL-BFM95 FAB-LMB96	Courses A → B COPAD; 2 courses given over 21 day interval	94% 98%
	Incompletely Resected	NHL-BFM95 FAB- LMB96	VA→B→ A→ B COP→ COPADM1→ COPADM2→ MiniCYVE1→ MiniCYVE2→ M1	94% 90%
Advanced Disease	NHL- BFM95	R3	VAA→ BB→ CC→ AA → BB	85%
		R4	VAA→ BB→ CC→ AA → BB → CC	81%
	FAB- LMB96	Group B	COP→ COPADM1 → COPADM2→ MiniCYVE1→ MiniCYVE2→ M1	90%
		Group C (CNS Negative)	COP→ COPADM1→ COPADM2→ CYVE1→ CYVE2→ M1→ M2→ M3 → M4	88%
		Group C (CNS Positive)	COP→ COPADM1→ COPADM2→ CYVE1→ HD-MTX→ CYVE2→ M1→ M2→ M3 → M4	83%

Table 1. Risk stratification used by different study groups

Protocol	Group	Definition	5yr. EFS
B-NHL (LMB89)	A	Completely resected stage-1 & abdominal stage-2	98%
	B	Unresected stage-1, non-abdominal stage-2 All stages 3 & 4 B-ALL < 70% Blast, CNS –ve	92%
	C	B-ALL > 70% Blast, CNS +ve	84%
B-NHL (BFM)	R1	Stage I, II Initial complete resection	94%
	R2	Stage 1, II Unresected, Stage III with LDH < 500U/L	94%
	R3	Stage III with LDH < 500-999U/L, BM+ve & LDH < 1000U/L	85%
	R4	LDH > 1000U/L and/or CNS +ve	81%

References:

1. Patte C, Auperin A, Michon J, et al: The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 97:3370-9, 2001

2. Reiter A, Schrappe M, Tiemann M, et al: Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 94:3294-306, 1999

3. Woessmann W, Seidemann K, Mann G, et al: The impact of the methotrexate administration schedule

and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood 105:948-58, 2005

4. Cairo MS, Gerrard M, Sposto R, et al: Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 109:2736-43, 2007

5. Patte C, Auperin A, Gerrard M, et al: Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood 109:2773-80, 2007

6. Gerrard M, Cairo MS, Weston C, et al: Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study. Br J Haematol 141:840-7, 2008

7. Arora B, Kaur U, Gulia S et al. Modified MCP-842: A novel highly efficacious, safe and cost-effective protocol for B-NHL treatment in resource poor countries. Proceedings of the third international symposium on childhood, adolescent and young adult Non-Hodgkin Lymphoma, June 2009, Frankfurt, Germany

Selected Abstracts:

1. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents.

Cairo MS, Gerrard M, Sposto R, et al.

Blood. 2007 Apr 1;109(7):2736-43.

The prognosis for higher risk childhood B-cell non-Hodgkin lymphoma has improved over the past 20 years but the optimal intensity of treatment has yet to be determined. Children 21 years old or younger with newly diagnosed B-cell non-Hodgkin lymphoma/B-cell acute lymphoblastic leukemia (B-NHL/B-ALL) with higher risk factors (bone marrow [BM] with or without CNS involvement) were randomized to standard intensity French-American-British/Lymphoma Malignancy B (FAB/LMB) therapy or reduced intensity (reduced cytarabine plus etoposide and deletion of 3 maintenance courses M2, M3, M4). All patients with CNS disease had additional high-dose methotrexate (8 g/m2) plus extra intrathecal therapy.

Fifty-one percent had BM involvement, 20% had CNS involvement, and 29% had BM and CNS involvement. One hundred ninety patients were randomized. The probabilities of 4-year event-free survival (EFS) and survival (S) were 79% +/- 2.7% and 82% +/- 2.6%, respectively. In patients in remission after 3 cycles who were randomized to standard versus reduced-intensity therapy, the 4-year EFS after randomization was 90% +/- 3.1% versus 80% +/- 4.2% (one-sided P = .064) and S was 93% +/- 2.7% versus 83% +/- 4.0% (one-sided P = .032). Patients with either combined BM/CNS disease

at diagnosis or poor response to cyclophosphamide, Oncovin [vincristine], prednisone (COP) reduction therapy had a significantly inferior EFS and S (P < .001). Standard-intensity FAB/LMB therapy is recommended for children with high-risk B-NHL (B-ALL with or without CNS involvement).

2. Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study.

Gerrard M, Cairo MS, Weston C, et al.

Br J Haematol. 2008 Jun;141(6):840-7.

High cure rates are possible in children with localized mature B-cell lymphoma (B NHL) using a variety of chemotherapeutic strategies. To reduce late sequelae, the duration and intensity of chemotherapy has been progressively reduced. The Lymphome Malins de Burkitt (LMB) 89 study reported long-term survival in almost all children with localized resected disease treated with two courses of COPAD (cyclophosphamide, vincristine, prednisolone and doxorubicin). This study was designed to confirm the effectiveness of this approach in a larger number of patients in a multinational co-operative study. The patient cohort was part of an international study (French-American-British LMB 96), which included all disease stages and involved three national groups. Patients in this part of the study had resected stage I or completely resected abdominal stage II disease. Following surgery, two courses of COPAD were given, without intrathecal (IT) chemotherapy. One hundred and thirty-two children were evaluable. Two of 264 (0.9%)

courses were associated with grade IV toxicity (one stomatitis and one infection). With a median follow up of 50.5 months, the 4 year event-free survival is 98.3% and overall survival is 99.2%. Children with resected localized B-NHL can be cured with minimal toxicity following two courses of low intensity treatment without IT chemotherapy.

3. Results of the randomized international FAB/ LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients.

Patte C, Auperin A, Gerrard M, et al.

Blood. 2007 Apr 1;109(7):2773-80.

A previous study (LMB89) of the French Society of Pediatric Oncology for childhood mature B-cell lymphoma (B-NHL) demonstrated a 92% 3-year event-free survival (EFS) for intermediate-risk group B defined as "non-resected" stage II/I and CNS-negative advanced-stage IIV/IV (70% of cases). We performed the FAB/LMB96 trial to assess the possibility of reducing treatment in children/adolescents with intermediate-risk B-NHL without jeopardizing survival. "Early responding" patients (tumor response > 20% at day 7) were randomized in a factorial design between 4 arms, 2 receiving half-dose of cyclophosphamide in the second induction course with cyclophosphamide, Oncovin (vincristine), prednisone, Adriamycin (doxorubicin), methotrexate (COPADM) and 2 not receiving the maintenance course M1. A total of 657 patients were randomized (May 1996 to June 2001) and 637 were analyzed. The analysis showed no significant effect of any of the treatment reductions on

EFS and survival. The 4-year EFS was 93.4% and 90.9% in the groups with full-dose and half-dose of cyclophosphamide (RR = 1.3, P = .40) and 91.9% and 92.5% in the groups with and without M1 (RR = 1.01, P = .98). There was no interaction between the 2 treatment reductions or between each treatment reduction and LDH level or histologic subtypes (Burkitt/Burkitt-like or large B-cell). Children/adolescents with intermediate-risk B-NHL who have an early response and achieve a complete remission after the first consolidation course can be cured with a 4-course treatment with a total dose of only 3.3 g/m2 cyclophosphamide and 120 mg/m2 doxorubicin.

4. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90.

Reiter A, Schrappe M, Tiemann M, et al.

Blood. 1999 Nov 15;94(10):3294-306.

In study NHL-BFM 90, we investigated whether the serum lactate dehydrogenase (LDH) concentration and early response are useful markers for stratification of therapy for childhood B-cell neoplasms in addition to stage, if the outcome of patients with abdominal stage III and LDH >/=500 U/L can be improved by high-dose (HD) methotrexate (MTX) at 5 g/m(2) instead of intermediate-dose (ID) MTX at 500 mg/m(2) in the preceding study 86; whether 2 therapy courses are enough for patients with complete resection; and whether combined systemic and intraventricular chemotherapy is efficacious for central nervous system-positive (CNS(+)) patients. After a cytoreductive prephase, treatment was stratified into 3 risk groups: patients in R1 (completely resected) received 2 5-day courses (ID-MTX, dexamethasone,

oxazaphorins, etoposide, cytarabine, doxorubicin, and intrathecal therapy), patients in R2 (extra-abdominal primary only or abdominal tumor and LDH <500 U/L) received 4 courses containing HD-MTX, and patients in R3 (abdominal primary and LDH >/=500 U/L or bone marrow/CNS/multilocal bone disease) received 6 courses. Incomplete responders after 2 courses received an intensification containing HD-cytarabine/etoposide. Patients with no or necrotic tumor thereafter received 3 more courses; 6 patients with viable tumor received autologous bone marrow transplantation. From April 1990 through March 1995, 413 evaluable patients were enrolled (R1, 17%; R2, 40%; and R3, 43%). The 6-year event-free survival (pEFS) was 89% +/- 2% for all and 100%, 96% +/-2%, and 78% +/- 3% in R1, R2, and R3, respectively. The pEFS of patients with abdominal stage III and LDH >/=500 U/L was 81% +/- 4% as compared with 43% +/- 10% in study 86. Of 26 CNS(+) patients, 5 died early, but only 3 relapsed.

5. The Société Française d'Oncologie Pédiatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia.

Patte C, Auperin A, Michon J, et al.

Blood. 2001 Jun 1;97(11):3370-9.

This study was undertaken to show that a high survival rate can be obtained in B-cell (Burkitt and large B-cell) lymphoma and L3 leukemia with multiagent chemotherapy adapted to the tumor burden (stage, resection status, percentage of blasts in bone marrow, and central nervous system [CNS] involvement) and early response to chemotherapy, to investigate actual

prognostic factors, and to see if large B-cell lymphoma can be treated with the same regimen as Burkitt lymphoma. Patients were classified into 3 risk groups. Group A (resected stage I and abdominal stage II) received 2 courses of vincristine, cyclophosphamide, doxorubicin, and prednisone. Group B (patients not eligible for groups A or C) received 5 courses of chemotherapy with, in addition, high-dose methotrexate, 3 g/m(2) over 3 hours; infusional cytarabine; and intrathecal (IT) methotrexate. Group C (patients with CNS involvement and acute lymphoblastic leukemia with at least 70% of blasts in bone marrow) received 8 courses with, in addition, high-dose methotrexate, 8 g/m(2); high-dose cytarabine; etoposide; and triple IT. Except in group A, treatment started with a prephase (COP, low-dose vincristine and cyclophosphamide). It was intensified for patients who did not respond to COP in group B and any patient with residual viable cells after the consolidation phase. A total of 561 patients were enrolled in the SFOP LMB89 protocol (July 1989-June 1996). Five-year survival is 92.5% (95% confidence interval [CI], 90%-94%) and event-free survival (EFS) 91% (95% CI, 89%-93%). EFS is 98% (95% CI, 90%-100%), 92% (95% CI, 89%-95%), and 84% (95% CI, 77%-90%) for group A, B, and C, respectively. In group B, multivariate analysis of prognostic factors showed that a lactate dehydrogenase level more than 2-fold the normal value, no response after COP, and age of at least 15 years were associated with a lower EFS. CNS involvement was the only prognostic factor in group C.

Pediatric Non-Hodgkin Lymphomas and Management of Lymphoblastic Lymphoma

Lymphoma (Hodgkin's and non- Hodgkin's) is the third most common childhood malignancy. Non- Hodgkin's lymphoma (NHL) accounts for approximately 7% of all cancers in children · Childhood NHL differs from adult NHL with respect to disease types, staging systems, biology, treatment, and outcome. While, NHL in adults is more commonly low or intermediate grade and nodal, almost all NHL that occurs in children is high grade, disseminated and extranodal. Childhood NHL is divided into four major categories which are detailed in table 1.

Staging of Pediatric Lymphomas:

Development of prognostically useful staging system in childhood NHL has been challenging because of unique biology, clinical behavior and outcome of four major subtypes of NHL in children. The Ann Arbor staging classification does not adequately reflect prognosis in childhood NHL. The St. jude is staging classification is used for pediatric NHL. (Table-2)

Table 1: Major biologic subgroups in childhood NHL

Histology	Immunology	Clinical Features	Cytogenetics
Burkitt and Burkitt-like	B- cell	Abdominal masses, GIT tumors, Waldeyer s ring	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)
Diffuse large B- cell	B –cell (germinal or post germinal center)	Abdominal masses, GIT tumors, Waldeyer s ring	t(8;14)(q24;q32) t(2;17)(p23;q23)
Anaplastic large cell	T cell, null cell or NK cell	Skin, nodes, bone lung	t(2;5)(p23;q35) t(1;2)(q25;p23)
Precursor T lymphoblastic	T cell t(10;14)(q24;q11)	Anterior mediastinal mass	t(1;14)(p32;q11) t(11;14)(p13;q11) t(7;19)(q35;p13)
Precursor B lymphoblastic	B cell precursors	Skin, lymph nodes	

Lymphoblastic lymphoma

Lymphoblastic lymphomas (LL) makes up approximately 30% of childhood NHL. 75% of LL have a T-cell immunophenotype(TLL). The remaining have a precursor B-cell phenotype (BLL). Both have different clinical features but treated similarly and have similar outcome

CLINICAL FEATURES

TLL usually presents with a rapidly enlarging neck and mediastinal lymphadenopathy (50 – 70 % cases). Anterior mediastinal mass causes signs / symptoms like cough, wheezing, orthopnoea, SVC obstruction(SVC syndrome). Sub diaphragmatic nodal presentation is rare. Testicular involvement is seen in less than 2 % cases.

BLL: It involves skin, bone, peripheral nodes. Sometmes cutaneous lesions typically in scalp are seen.

Table-2 Comparison of Murphy and Ann Arbor staging systems for non-Hodgkin's lymphoma

Stage	Murphy	Ann Arbor
Stage	I single extranodal tumor or single anatomic nodal area with exclusion of mediastinum and abdomen	Single lymph node region or extranodal site (IE)
Stage II	A single extranodal tumor with regional nodal involvement e"2 nodal or extranodal tumors on the same side of the diaphragm A primary gastrointestinal tract tumor that is completely resected	e" 2 involved nodal regions or localized involvement of extranodal disease (IIE) on the same side of diaphragm
Stage III	e" 2 nodal or extranodal tumors on ooposite sides of the diaphragm Any primary intrathoracic tumor Unresectable primary intra-abdominal disease Any paraspinal or epidural disease	Nodal or localized extranodal involvement (IIIE) on both sides of diaphragm
Stage IV	Involvement of central nervous system and/or bone marrow	Diffuse or disseminated involvement of one or more extranodal sites or organs

Diagnostic Evaluation: The least invasive procedure should be used to establish the diagnosis such as pleurocentesis, lymphonode biopsy or bone marrow aspiration. Any invasive diagnostics may be dangerous and should, be postponed in patients with upper vena cava syndrome and respiratory distress due to a mediastinal tumor. In such cases, immediate treatment with corticosteroids, potentially combined with cyclophosphamide, for up to 48 hours is beneficial and unlikely to obscure subsequent pathologic diagnosis. Critical pleural or/and pericardial effusions require drainage and may enable comprehensive diagnostics.

Cytomorphology, histomorphology, and immunophenotyping are basic diagnostic methods.

Morphology – monomorphic small cell population with high mitotic rate.

Immunophenotype – CD 10 +, CD 79 a +, CD 20 - /+, TdT + in BLL , Cytoplasmic CD 3 +, CD 4 +, CD 5 +, CD 7 +, CD8 +, TdT + in TLL.

Cytogenetics - Chromosomal abnormalities are not well characterized in patients with lymphoblastic lymphoma. However, one study demonstrated that loss of heterozygosity on chromosome 6q in T-cell lymphoblastic lymphoma patients was associated with an increased risk of relapse. (Level of evidence IVC)

Staging work up and staging: Patients with Lymphoblastic lymphomas are staged as per St Jude staging system. St Jude system is, however, redundant for LL as most patients present with stage III or IV. Apart from complete blood counts and liver/ renal functions, LDH; patients should undergo bone marrow aspirate & biopsy, lumber puncture and CT scan of primary site along with CT thorax & abdomen. Role of PET-scan in

the evaluation of status of residual mediastinal mass after induction is investigational.

The difference between lymphoma with involvement of the bone marrow versus leukemia is arbitrary. Traditionally, patients with more than 25% marrow blasts are considered to have leukemia, and those with fewer than 25% marrow blasts are considered to have lymphoma. It is not yet clear whether these arbitrary definitions are biologically distinct or relevant for treatment design. CNS disease in lymphoblastic lymphoma is defined by criteria similar to that used for acute lymphocytic leukemia (i.e., white blood cell count of at least 5/μL and malignant cells in the cerebrospinal fluid [CSF]). Overall, CNS involvement was diagnosed in 3-6% of patients.

Management

Therapeutic protocols used for ALL, which are based on the principle of continual exposure to cytostatics over a long period of time, are efficacious for treating children with LBL, this was proved by COG -5026 trial that randomized children with NHL to COMP (cyclophosphamide, vincristine, intermediate dose methotrexate, prednosolone) or to a modified LSA2L2 regimen. In this study patients with advanced LL fared better when treated with LSA2L2 regimen, EFS 74 % vs. 64 %. In large, multicenter studies, EFS rates of 60% to more than 80% were achieved, for children with advanced-stage T-LBL (Table 3).

Currently, the most frequently used treatment regimens are the LSA2-L2 protocol in numerous modified forms and the Berlin-Frankfurt-Munster (BFM) group strategy. Both protocols are divided into phases of induction, consolidation, reintensification, and maintenance. The

main differences between the protocols are earlier application of L-Asp and high dose (HD) MTX (5 g/m^2 intravenous over 24 hours) in the BFM regimen. Treatment duration for both regimens was 18 to 24 months. Repeated continuation courses, including CP and anthracycline until the end of therapy, are part of the LSA2-L2 protocol, while maintenance includes only oral 6-MP and MTX in the BFM strategy. The NHL- BFM 90 –LBL study has shown that with intensive ALL-type chemotherapy including moderate cumulative doses of anthracyclines 240 mg/m2 and cyclophosphamide (3 g/ m2) and moderate dose prophylactic cranial irradiation but no Local radiotherapy, an event-free survival rate of 90% can be achieved in childhood T -LBL.

The contribution of individual drugs to patient cure is largely unknown. For L-Asparginase, the effect in T-LBL was demonstrated in the POG-8704 trial, when patients did or did not receive weekly L-Asparginase after induction. Complete remission rate was 78 % for those who received L-asparginase versus 64 % for those who did not. Within BFM protocols, no additive effect on outcome was observed for HD cytarabine in the consolidation phase. Most studies advocate 24 months of therapy for TLL ,but the relapse pattern in BFM -90 study suggest that the duration of therapy can be reduced to 18 months.

Stratification of treatment intensity

Treatment intensity is mainly stratified according to stages I and II (early LL) versus stages III and IV(advanced LL).

Early LL: Children with stage I/II are rare. Most have pB-LBL and achieve EFS rates higher than 90% with reduced- intensity (omission of reintensification in the

Table-3 : Results of recent multicenter studies on childhood lymphoblastic lymphoma

			Stages (St. Jude staging system) No. of patients / pEFS				
Study	**No. of patients**	**pEFS at 3-5 yrs**	**I**	**II**	**III**	**IV**	**Comments**
CCG- 502	281	NG	-	I+II 28/ 84%	219/70%	34/46%	Randomized trial Modified LSA2-L2 vs ADCOMP EFS 74% vs 64%
POG -8704 weekly	180	NG	NE	NE	NG	NG	Randomized trial: 20 L-Asp vs no L-Asp . 4-y pCCR 78 vs 64%
NHL-BFM90-LBL	105	90 %	2/100%	2/100 %	82/90%	19/95%	T-LBL only
NHL-BFM95-LBL	198	80 %	-	I+II 22/ 95%	123/79%	53/77%	Omission of pre-emptive cranial irradiation
SFOP-backbone, LMT96	83	87 %	NG	NG	NG	NG	T-LBL only, BFM-early intensification day 8

BFM protocol) and 24 Weeks of maintenance therapy. (Level of evidence 1 B)

In a study by Link et al, the EFS among patients with early-stage LL was inferior in comparison with non LL lymphoma (63% vs. 88%, P<0.001). It became apparent that among patients with lymphoblastic lymphoma, those who receive eight months of chemotherapy (including six months of continuation chemotherapy with or without radiotherapy) have a better outcome than those who receive nine weeks of chemotherapy without continuation chemotherapy. Thus a 24-week maintenance in addition to a 9- week induction was found beneficial for patients with LBL. This suggests that biological similarity to ALL is more important for LL than their low tumor burden and that they might, therefore, benefit from an ALL-type treatment, including maintenance.

Advanced LL: Currently, the most frequently used treatment regimens are the LSA2-L2 protocol in numerous modified forms and the Berlin-Frankfurt-Munster (BFM) group strategy. Both protocols are divided into phases of induction, consolidation, reintensification, and maintenance. These children with advanced LL require 18 -24 months of therapy. (Level of evidence 1B)

Role of Local RT (LRT) & Local Surgery :

The BFM-90 protocol assessed relevance of persistent thoracic disease at end of induction. The study showed EFS at 5 years of 95% ± 2% for the 80 patients with complete tumor response at the end of induction, and 89% ± 5% for 19 patients with tumor remnants after induction. All those who had tumor remnants underwent surgery and only necrotic material was documented. Of 19 Patients with tumor residues after induction,

2 relapsed as compared to 4 of 80 patients with complete tumor regression. Hence, Initial therapy predicts outcome irrespective of persistent abnormalities on CXR. Most often residual mass is necrotic and there is no role for local surgery or local RT in the consolidation for such patients to prevent local relapse. Even in patients with testicular disease at diagnosis, testicular radiation is only indicated for residual disease that is biopsy proven after systemic therapy incorporating high-dose MTX. (Level of evidence 1 B).

Extracompartmental therapy.

CNS negative patients: For CNS-negative patients, treatment that includes intrathecal MTX and systemic HD MTX (0.5-5 g/m²) but no CRT is sufficient CNS protection. In NHL-BFM-95, prophylactic cranial radiation was omitted for CNS negative patients with stages III and IV LBL and intensity of induction therapy was modified (dose of daunorubicin & asparaginase reduced). There was no significant increase in CNS relapse, suggesting that cranial radiation may be reserved for patients with CNS disease at diagnosis. (Level of evidence 1 B)

CNS positive patients: 18 to 24 Gy cranial irradiation (CRT), in addition to LSA2-L2 or BFM chemotherapy, is highly effective in preventing CNS recurrences [¨] (Level of evidence 1 B). The dose of CRT 18 Gy in the second year of life and 24 Gy in older children. Infants under 1 year of age not irradiated.

Emerging strategies in the management

Stage appears to be a poor indicator of outcome in pediatric LL, and dose intensification has not resulted in improved outcome. Therefore, biologic markers are

needed to improve risk stratification. In studies of adult patients with precursor T-cell lymphoid malignancies (T-cell ALL and T-cell LL) *HOX11* activation has been associated with improved prognosis, whereas *TAL1* and *LYL1* expression have been associated with worse outcome However, results such as these require validation in studies of pediatric LL.

Studies in T-cell ALL have demonstrated that the inability to clear MRD during induction is highly predictive of poorer outcome and that the amount of MRD in peripheral blood correlates with disease in the marrow.It was recently demonstrated that peripheral blood is at least as good as marrow at detecting and following MRD in pediatric LL patients. It has been shown that both flow cytometry and RQ-PCR methods are efficient for MDD and MRD analyses in T-LL · These tests could distinguish patients with or without disease dissemination among those with stage II/III disease, a parameter that, together with MRD measurements in peripheral blood, might become useful for risk assignment in future regimens · Whether the inability to clear MRD in LL will identify patients with high risk for treatment failure remains unclear.

Suggested Readings

1. Alfred Reiter, Martin Schrappe, Wolf-Dieter Ludwig et al : Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM Group report. Blood. 2000;95: 416-421

2. Birgit Burkhardt, Wilhelm Woessmann, Martin Zimmermann et al Impact of Cranial Radiotherapy on Central Nervous System Prophylaxis in Children and Adolescents With Central Nervous System–

Negative Stage III or IV Lymphoblastic Lymphoma. J Clin Oncol.2006 ; 24 :491-499

3. Bergeron C, Celine S, Pacquement H, et al. Childhood T-celllymphoblastic lymphoma (TLL) Results of the SFOP LMT96 strategy. Pediatr Blood Cancer. 2006; 46 :967

4. Link MP, Shuster JJ, Donaldson SS, Berard CW, Murphy SB. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. N Engl J Med. 1997;337:1259–1266.

5. Elaine Coustan-Smith, John T. Sandlund, Sherrie L et al : Minimal Disseminated Disease in Childhood T-Cell Lymphoblastic Lymphoma: A Report From the Children's Oncology Group. J Clin Oncol. 2009 ; 27:3533-3539.

Selected Abstracts

1. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma

Link MP, Shuster JJ, Donaldson SS, et al.

N Engl J Med. 1997;337:1259–1266

Between 1983 and 1991, two consecutive trials in children and young adults (age, d" 21 years) with early-stage non-Hodgkin's lymphoma were conducted. In the first trial, patients were treated for 9 weeks with induction chemotherapy consisting of vincristine, doxorubicin, cyclophosphamide, and prednisone, followed by 24 weeks of continuation chemotherapy with mercaptopurine and methotrexate.Half the patients were randomly assigned to receiveinvolved-field irradiation. In the second trial, after the 9 weeks of induction chemotherapy, the patients were randomly assigned to

receive 24 weeks of continuation chemotherapy or no further therapy.

Results A total of 340 patients were enrolled in the two trials, 12 of whom did not have complete remissions. One hundred thirteen patients received nine weeks of chemotherapy without radiotherapy,131 received eight months of chemotherapy without radiotherapy, and 67 received eight months of chemotherapy with radiotherapy. At five years, the projected rates of continuous complete remission were 89, 86, and 88 percent for the three groups, respectively. At five years, event-free survival among the patients with early-stage lymphoblastic lymphoma was inferior to that among the patients with other subtypes of lymphoma (63 percent vs. 88 percent ,P< 0.001). Continuation therapy was effective only in patients with lymphoblastic lymphoma.

Conclusions A nine-week chemotherapy regimen without irradiation of the primary sites of involvement is adequate therapy for most children and young adults with early-stage, non lymphoblastic non-Hodgkin's lymphoma

2. Comparison of treatment regimens for pediatric lymphoblastic non-Hodgkin's lymphoma: a Childrens Cancer Group study

Tubergen DG, Krailo MD, Meadows AT, Rosenstock J et al.

J Clin Oncol. 1995 Jun;13(6):1368-76

Purpose: Patients with lymphoblastic non-Hodgkin's lymphoma (LB NHL) were randomized to treatment with either modified LSA2L2 or ADCOMP, which added daunorubicin (DAUN) and asparaginase (L-ASP) to the methotrexate (MTX), cyclophosphamide (CYT), vincristine (VCR), and prednisone (PRED) (COMP)

regimen, in a clinical trial to determine the relative effectiveness and toxicity of the two regimens.

Patients and Methods: Patients with LB NHL were eligible for this randomized study if they were less than 22 years of age at diagnosis and had < or = 25% blasts in the bone marrow. Of 307 patients registered, 281 were fully eligible and assessable. Patients were stratified by extent of disease at diagnosis.

Results: The 5-year event-free survival (EFS) rate for patients with localized disease was 84%, and for patients with disseminated disease, 67%. There were four relapses in 28 patients with localized disease. Two hundred six patients had mediastinal primary tumors and despite local radiation, 34 of 63 failures in these patients involved the primary tumor site with or without other involvement. After adjusting for extent of disease at diagnosis, the regimens did not differ significantly with respect to risk for adverse events. The acute toxicity was primarily neutropenia and thrombocytopenia, with greater initial toxicity in patients on the LSA2L2 regimen. Three patients developed acute myelogenous leukemia.

Conclusion: Long-term EFS in children with LB NHL can be achieved in the majority of patients. Disease progression, which includes recurrence at the primary tumor site, is a major cause of treatment failure in patients with mediastinal presentations. Addition of DAUN and L-ASP to the COMP regimen does not produce a more effective treatment than LSA2L2.

3. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM Group report.

Alfred Reiter, Martin Schrappe, Wolf-Dieter Ludwig, et al

Blood. 2000;95: 416-421

The purpose of our study was to investigate the efficacy of an acute lymphoblastic leukemia (ALL)-type treatment with moderate-dose, prophylactic cranial irradiation and without local radiotherapy for childhood T-cell lymphoblastic lymphoma (T-LBL). From April 1990 to March 1995, 105 evaluable patients, 1.1 to 16.4 years of age, with T-LBL were enrolled in study NHL-BFM 90 (non-Hodgkin's lymphoma–Berlin-Frankfurt-Munster 90). They received an 8-drug induction over 9 weeks followed by an 8-week consolidation including methotrexate (MTX) 5 g/m2 3 4. Patients with stage I (n 5 2) and II (n 5 2) continued with maintenance therapy (6-mercaptopurine daily and MTX weekly, both orally) until a total therapy duration of 24 months. Patients with stage III (n5 82) and IV (n 5 19) received an 8-drug intensification over 7 weeks and cranial radiotherapy (12 Gy for prophylaxis) after consolidation, followed by maintenance. Residual tumor after induction had to be resected. Patients received intensified chemotherapy if tumor regression on day 33 of induction was less than 70% or when vital residual tumor was present after the complete induction phase. With a median follow-up of 4.5 years, the estimated event-free survival at 5 years is 90% (95% confidence interval, 82%-100%).

Events were 1 early death, 8 tumor failures, and 1 secondary acute myeloid leukemia. A total of 101 patients were evaluable for the speed of tumor response. Two patients received intensified therapy due to less than 70% tumor regression on day 33. Of 19 patients with tumor residues after induction, 2 relapsed as compared to 4 of 80 patients with complete tumor regression. We conclude

that, with intensive ALL-type chemotherapy including moderate cumulative doses of anthracyclines 240 mg/m2 and cyclophosphamide (3 g/m2) and moderate dose prophylactic cranial irradiation but no local radiotherapy, an event-free survival rate of 90% can be achieved in childhood T -LBL.

4. Impact of Cranial Radiotherapy on Central Nervous System Prophylaxis in Children and Adolescents With Central Nervous System–Negative Stage III or IV Lymphoblastic Lymphoma

Birgit Burkhardt, Wilhelm Woessmann, Martin Zimmermann, et al.

J Clin Oncol.2006 ; 24 :491-499.

Purpose: In the Non-Hodgkin's Lymphoma–Berlin-Frankfurt-Munster (NHL-BFM) 95 trial, we tested, against the historical control of the combined trials NHL-BFM90 and NHL-BFM86, whether prophylactic cranial radiotherapy (PCRT) can be omitted for CNS-negative patients with stage III or IV lymphoblastic lymphoma (LBL) with sufficient early response.

Patients and Methods: Apart from the removal of PCRT in NHL-BFM95, the chemotherapy of the three trials was identical except for the amount of L-asparaginase and daunorubicin during induction. The therapy inNHL-BFM95 was accepted to be non inferior when compared with trials NHL-BFM90/86 if the lower limit of the one-sided 95% CI for the difference in the 2-year probability of event-free survival(pEFS) between target patients of NHL-BFM95 and the historical controls of NHLBFM90/86 did not exceed _14%. The target patient group consisted of stage III and IV patients who were CNS negative and responded well to induction therapy.

Results: The number of target patients was 156 in NHL-BFM95 (median age, 8.6 years; range, 0.2 to 19.5years) and 163 in NHL-BFM90/86 (median age, 8.4 years; range, 0.6 to 16.6 years). For the target group, the pEFS rates at 2 and 5 years were 86% and 82% respectively, inNHL-BFM95 (median follow-up time, 5.1 years; range, 2.1 to 9.1 years) compared with 91% and 88%, respectively in NHL-BFM90/86 (median follow-up time, 10.7 years; range, 5 to15.4 years). The lower limit of the one-sided 95% CI for the difference in pEFS was 11% at 2years and 13% at 5 years. In NHL-BFM95, one isolated and two combined CNS relapses occurred compared with one combined CNS relapse in NHL-BFM90/86. Five-year disease-free survival rate was 88% in NHL-BFM95 compared with 91% in NHL-BFM90/86.

Conclusion: For CNS-negative patients with stage III or IV LBL and sufficient response to induction therapy, treatment without PCRT may be non inferior to treatment including PCRT.

Management of Pediatric Anaplastic Large Cell Lymphoma (ALCL)

ALCL is one of the most fascinating as well as enigmatic disease with myriad clinical presentations. It constitutes approximately 10-15% of all paediatric NHLs. A considerable majority (65%) display T-cell markers while rest are Null-cell type. Diagnostic criteria are now well established. ALCL is characterized by the proliferation of large pleiomorphic cells of a T/null phenotype that tend to invade the lymph node sinuses and express the CD30 antigen. In children, most ALCLs exhibit a t(2;5) translocation, which can be detected by anaplastic lymphoma kinase (ALK) antibodies. The existence of B-cell ALCL (B-ALCL) and Hodgkin-like ALCL has been a matter of debate for years, but these lymphomas were excluded from ALCL in the recent classifications (Revised European-American Lymphoma [REAL] and World Health Organization classifications).

Clinical features:

The most common clinical features include a generalized adenopathy with the frequent presence of B symptoms

and involvement of extra nodal sites such as the skin (21%), soft tissues (17%), bones (17%), lung (11%) and liver (8%).The central nervous system (CNS) and bone marrow are rarely involved. ALCL occurs as two distinct clinical entities, a primary cutaneous (PCALCL) and a systemic variant. PCALCL can be confused with systemic ALCL, which often involves the skin. Thus all patients with suspected PCALCL should have complete staging to rule out systemic involvement. One useful distinction is the fact that PCALCL rarely has t(2;5) or variant translocations, and therefore generally does not express ALK, whereas systemic ALCL often does. Thus a patient with cutaneous ALCL lesions that are ALK+ should be considered to have systemic disease until proven otherwise. Furthermore, PCALCL often expresses cutaneous lymphocyte antigen (CLA) but does not express epithelial membrane antigen (EMA), whereas the converse is generally true in systemic ALCL.In contrast to PCALCL, systemic ALCL is generally very aggressive. The majority of patients present with stage III or IV disease and have systemic symptoms.

Workup

For confirmation of diagnosis, staging and therapeutic planning, following tests are required;

- Blood tests: Complete blood count, Liver function test, Renal function test, Serum electrolyte, Calcium, Phosphorus, Uric acid, LDH, ESR, HIV
- Diagnostic biopsy for Histopathology/ Immunophenotype/ genetic analysis or pleural fluid/ ascitic fluid for cytological diagnosis if present.
- Bone marrow aspiration and biopsy

- CSF analysis
- Radiological tests: CT/MRI of the primary site and thorax, abdomen, and pelvis. PET-CT may be potentially useful for assessing the speed of response and confirmation of post-therapy remission (CR) but is currently not standard of care.

Staging and Risk Stratification:

The staging should be as per St.Jude's children's research hospital staging classification. However, it does not apply to ALCL because of frequent presence of non-CNS and bone-marrow extra-nodal (85%) disease. Hence, risk-stratified treatment which reflects, outcome is becoming more acceptable for treatment planning in ALCL. Individually, no clear prognostic factors have emerged in past studies due to small number of patients. Recently, culled data from 3 major European cooperative groups has revealed 3 major adverse prognostic factors which include skin involvement, mediastinal involvement and visceral disease (lung, spleen or liver). (Table 1). Studies in adults, have shown that the most important prognostic factor in systemic ALCL was the presence or absence of the ALK protein. The importance of the IPI was also demonstrated in an Italian series in which ALK+ patients with a low or low–intermediate IPI score had a 5-year OS rate of 94%, whereas ALK+ patients with a

Table 1. Risk stratification currently used for Pediatric ALCL

ALCL-99 stratification (SFOP,BFM UKCCSG)	Low risk	Stage 1 completely excised	90% EFS (5 yr)
	Stand. Risk	No skin, mediastinal, liver, spleen, lung involvement	90% EFS (5 yr)
	High risk	Biopsy proven skin, mediastinal, liver, spleen, lung involvement.	60% EFS (5 yr)

high-intermediate or high IPI score had a 5-year OS rate of only 41%.

Management of ALCL

Systemic ALCL, like Burkitt's lymphoma, has a high growth fraction (>90%) and hence has aggressive clinical behaviour. A substantial majority (75%) have B-symptoms and extra nodal involvement (60%). Intriguingly, bone marrow (< 10%) and CNS (<5%) involvement is relatively uncommon. Hence, most protocol treat ALCL like B-NHL. However, some treat like lymphoblastic lymphoma

Meaningful conclusions regarding management of ALCL are difficult to draw from published series due to small number of patients, significant heterogeneity in inclusion criteria, variable staging system used and diverse treatment approaches in various series. The therapy of ALCL differs depending on whether a patient has the cutaneous or systemic variant

Cutaneous ALCL

PCALCL is an indolent disease; treatment should focus on minimally invasive local therapies. Systemic therapies should be reserved for patients with disseminated disease or disease that is refractory to local measures. There are essentially no large series examining the efficacy of local therapy in PCALCL, but anecdotal observations and small case reports suggest that long-term remissions can be achieved with surgical excision and/or localized radiotherapy. Low-dose, single-agent methotrexate is an effective therapy for PCALCL in patients with widespread cutaneous disease or in those whom radiation and surgery have failed.

Systemic ALCL

No standard therapeutic regimen exists for the treatment of ALCL; however, following broad principles can be derived from published data.

A) Protocol: - In view of high growth fraction; aggressive multiagent intensive regimens should be used. Majority of European groups e.g.:- BFM, SFOP, UKCCSG have used short duration pulse intensive B-cell type approach with good results while American (CCG, POG) and Italian groups (AIEOP) have used T-cell type long duration less intensive approach with almost equivalent survival. However, shorter duration, lesser cost of treatment and lower cumulative doses of chemotherapeutic agents especially alkylators and antracyclines favour short duration B-cell type approach.

Results of different national protocols

BFM Studies

The result of the BFM studies on 87 patients treated with the protocols NHL BFM-90 have been reported by Reiter et al. All the patients received a prephase with vincristine, cyclophosphamide and dexamethasone, then the treatment was stratified according to stage:

- Stage 1 & 2 resected received 3 courses : one course 'a'(Methotrexate 500mg/m^2 in continuous infusion over 24 hours, Ifosfamide 800 mg/m^2 X 5, VP-16 100 mg/m^2 X 2, Cytarabine 150 mg/m^2 X 2, Dexamethasone 10 mg/m^2 X 5 and triple intrathecal treatment Prednisolone, Methotrexate & Cytarabine) and a course 'b' (Dexamethasone, Methotrexate and Cytarabine, Cyclophosphamide 200 mg/m^2 X 5, Adriamycin 25 mg/m^2 X 2) followed by second course of 'a'.

- Stage 2 not resected and stage 3 received 6 courses (3 courses 'a' and 3 courses 'b' given alternately, the duration of treatment being 4 months. A total dose of Adriamycin 150 mg/m^2, of Cyclophosphamide 3.4 gm/m^2, of Ifosfamide 12 gm/m^2 was given.
- Stage 4 defined by the existence of multifocal bone disease and/or BM disease and/or CNS involvement received 2 courses AA (identical to course 'a' but with a dose of methotrexate of 5 gm/m^2 and an injection of vincristine),2 courses BB (identical to 'b' but with a dose of methotrexate of 5 gm/m^2 and an injection of vincristine) and a 2 courses of 'CC' (Dexamehasone, Vincristine, Cytarabine 2 gm/m^2 X 4, Etoposide 150 mg/m X 3 and intrathecal therapy)

SFOP studies

SFOP conducted two consecutive studies for ALCL : HM89 & HM91

- Study HM89: This study used intensive induction treatment of 1 COP and 2 COPADM and maintenance treatment consisting of 4 cycles of 2 courses VEM (VP-16, Cyclophosphamide, Methotrexate) and VAD (Vincristine, Adriamycin) for duration of 8 months.
- Study HM 91 : This study used intensive induction treatment of 1 COP and 2 COPADM, then maintenance treatment consisting of 4 cycles of 2 courses : VEBBP (Vinblastine,VP-16,Bleomycin, Prednisone) and sequence 1 (Methotrexate, Vincristine, Doxorubicin, Cyclophosphamide and Prednisone) for duration of 7 months.

Italian study

- The AIEOP protocol LNH consisted of an induction and consolidation similar to those of the protocol LSA_2L_2, followed by a maintenance treatment consisting of 7 cycles of 4 weekly courses given alternatively using Cyclophosphamide, 6MP, Cytarabine-VP16 and Vincristine-Dexamethasone
- Stage 3 & 4 received in addition triple intrathecal treatment every 6 weeks. Duration of treatment was 24 months. At 19 months follow up, the EFS was 65%, however several relapses occurred later on reducing the EFS.

UK studies

- Intensive induction treatment with COP and 2 COPADM, followed by 2 CYM (Cytarabine, Methotrexate) and a final COPADM is used. Duration of treatment was 5 months.

COG studies

- COG study consisted of a induction treatment with doxorubicin 75mg/m2 day 1 and 22, vincristine 1.5mg/m2 day 1 and 22, prednisone 40 mg/m2 daily for 28 days, and age adjusted intrathecal methotrexate on days 1, 8, and 22, followed by two different maintenance regimen for 12 months.Maintanance regimen for Arm 1 consisted of APO maintenance (doxorubicin 30 mg/m2 and vincristine 1.5 mg/m2 on day 1, prednisone 120 mg/m2 and 6-mercaptopurine 225/mg/m2 days1to5) given every 21 days. For Arm 2 maintenance regimen consisted of APO maintenance(as given in arm 1) alternating with Intermediate dose

methotrexate (IDM)/HiDAC; IDM 1 g/m2 over 24 hours followed by cytarabine 500 mg/m2 bolus, and continuous infusion of cytarabine 60 mg/m2 over 48 hours every 21 days. Both maintenance arms included intrathecal methotrexate on day one of maintenance cycles 1, 3, and 5, and doxorubicin was substituted with methotrexate after a cumulative dose of 300 mg/m2 was reached.

The overall survival (OS) and event free survival (EFS) appear significantly different between 3 major national groups as in the table below (Table -2)

Table -2 : Outcomeof ALCL in EUROPE

Outcome	BFM (93 pts)	S.F.O.P (82pts)	U.K.C.C.S.G (60 pts)	P
3-year EFS	79%(70-86%)	67%(56-77%)	55%(42-68%)	0.005
3- year OS	90%(82-95%)	83%(73-91%)	64%(51-76%)	$<10^{-5}$

The above data suggests that :

i. Best results are obtained with the BFM protocol which is less intense than the French one, both in terms of duration and cumulative dose of Cyclophosphamide and Adriamycin.

ii. Treatment should be stratified according to risk factors,i.e patients with skin and/or mediastinal and/ or visceral involvement should be classified as a high risk group.

iii. Rare patients with stage I completely resected may be treated with short chemotherapy protocol

Based on the above insights, multinational ALCL-99 was planned which is detailed below;

ALCL-99

The ALCL-99 protocol, based on the Non-Hodgkin's Lymphoma Berlin-Frankfurt-Muenster 90 (NHL-BFM90) study protocol, looked at the impact of :

1. **The dose and scheduling of methotrexate** (R1 randomisation) – They compared six courses of methotrexate 1 g/m2 over 24 hours and an intrathecal injection (IT) followed by folinic acid rescue at 42 hours (MTX1 arm) with six courses of methotrexate 3 g/m2 over 3 hours followed by folinic acid rescue at 24 hours without IT (MTX3 arm)
2. **The benefit of addition of vinblastine during induction chemotherapy and as a maintenance** (R2 randomisation)

The results of the R1 randomisation showed that the methotrexate schedule of the NHL-BFM90 protocol could be safely replaced by a less toxic schedule of methotrexate 3 g/m2 in a 3-hour infusion without IT therapy. Recent analysis from ALCL-99 suggests that there is no benefit of addition of Vinblastine (under Publication).

MCP-842

This protocol consisted of eight alternating cycles of two regimens, A (Cyclophosphamide, Adriamycin, Vincristine and Cytosine-arabinoside) and B (Etoposide, Vincristine, Methotrexate, and Ifosfamide). Intrathecal methotrexate and cytosine arabinoside were administered in the first 4 cycles. From 2004 onwards, Vincristine was replaced by Vinblastine (modified MCP-842). No radiotherapy or high dose methotexate was given in this protocol. The EFS increased from 43% to 75%, OS increased from 68% to 88% and relapse rate decreased from 31.5% to

12.5% after addition of Vinblastine in place of Vincristine in modified MCP-842 protocol.

B) Role and experience with Vinblastine

Vinblastine is the most potent drug in-vitro against the ALCL cells. One of the most commonly used second line treatment for ALCL consists of combination of Vinblastine, CCNU and Bleomycin or Vinblastine, CCNU and Cytarabine. In these two protocols, Vinblastine is given weekly. In a French series of patients with ALCL, 25/28 patients treated with these protocols at relapse achieved a second remission and with a median follow up of 30 months, 16 were still alive in CR with or without ABMT. The treatment of weekly Vinblastine alone for 6 months to 2 years (median-1 year) to 13 relapsed French patients including 6 relapses after ABMT was found to be succesful .10/11 patients achieved CR and 8 are alive and disease free with a median follow up of 30 months since the beginning of Vinblastine. However, the ALCL-99 study has shown that the addition of vinblastine in the upfront treatment appears to have only delayed the time to relapse and there was no difference in EFS at 2 yrs after the end of therapy. (under Publication)

C) CNS Prophylaxis

Cranial prophylaxis using high or intermediate dose methotrexate with intrathecal (BFM) or without intrathecal (SFOP,ALCL-99) or only intrathecal therapy (COG, MCP-842) have shown equivalent results with less than 1% incidence of CNS relapses. Hence, either high dose methotrexate at 3 gm/m^2 over 3 hour infusion or intrathecal therapy alone should be used for CNS prophylaxis. Cranial radiotherapy (RT) is not recommended (Level of evidence-IIA)

Treatment for patients with CNS involvement

As discussed earlier, CNS involvement is exceptional and if present should be treated according to protocol designed for B-lymphoma with CNS involvement; usually with radiation therapy.(Level of evidence III B)

D) Risk Stratified Management of Systemic ALCL

Standard Risk: - Stage I/II completely resected with no high risk features including involvement of skin, mediastinum, visceral organs (Liver, spleen, and lung), CNS or bone marrow.

These can be managed with 3 cycles (10-12 weeks) of pulse intensive B-cell type regimen (like ALCL-99). In centres without the experience of high dose methotrexate administration, modified MCP-842 with Vinblastine in place of Vincristine may be considered. (level of evidence-IIA)

High Risk: - All non-standard risk patients qualify for high risk group. These can be managed by 6 cycles (6 months) of short duration B-cell type regimen (ALCL-99). In centres without the experience of high dose methotrexate administration, Modified MCP-842 may be considered. (Level of evidence IIA)

Response Evaluation: - All patients should undergo response evaluation with clinical examination and conventional imaging at the end of 2 cycles for response evaluation. Patients with suboptimal response (stable disease/progression) should be considered for salvage treatment. Patients with good response should complete the treatment and undergo post treatment revaluation.

Suggested Reading:

1. Stein H, H. D. Foss, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000;96(12): 3681-95

2. Le Deley L.Prognostic factors in ALCL. Ann Oncol 1999(abstract);10:0

3. Jacobsen E. Anaplastic large-cell lymphoma, T-/ null-cell type. Oncologist. 2006 ;11(7):831-40

4. Brugières L, Deley MC, Pacquement H, et al.: CD30(+) anaplastic large-cell lymphoma in children: analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. Blood 1998;92 (10): 3591-8

5. Seidemann K, Tiemann M, Schrappe M, et al.: Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood 2001;97 (12): 3699-706

6. Laver JH, Kraveka JM, Hutchison RE, et al.: Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. J Clin Oncol 2005; 23 (3): 541-7,

7. Brugie'res L, Le Deley, Rosolen A, et al. Impact of the Methotrexate Administration Dose on the Need for Intrathecal Treatment in Children and Adolescents With Anaplastic Large-Cell Lymphoma

Results of a Randomized Trial of the EICNHL Group. J Clin Oncol,2009; 27:897-903

8. Banavali SD, Arora B, Vora T, Bansal S, Hingmire S, Pai SK, , Parikh PM, Kolhatkar B, Adde M, Magrath I. Vinblastine improves outcome in children with anaplastic large cell lymphoma (alcl) treated with a uniform short duration intensive protocol. SIOP XXXIX meeting Abstracts PJ038. Pediatr Blood Cancer , 2007; 49:532

9. Brugières L, Quartier P, Le Deley MC, et al.: Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children—a report from the French Society of Pediatric Oncology. Ann Oncol 2000;11 (1): 53-8.

Selected Abstracts:

1. Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90.

Seidemann K, Tiemann M, Schrappe M, et al

Blood. 2001 Jun 15;97(12):3699-706.

Anaplastic large-cell lymphoma (ALCL) accounts for approximately 10% of pediatric non-Hodgkin lymphoma (NHL). Previous experience from NHL-Berlin-Frankfurt-Münster (BFM) trials indicated that the short-pulse B-NHL-type treatment strategy may also be efficacious for ALCL. The purpose of this study was to test the efficacy of this protocol for treatment of childhood ALCL in a large prospective multicenter trial and to define risk factors. From April 1990 to March 1995, 89 patients younger than

18 years of age with newly diagnosed ALCL were enrolled in trial NHL-BFM 90. Immunophenotype was T-cell in 40 patients, B-cell in 5, null in 31, and not determined in 13. Stages were as follows: I, n = 8; II, n = 20; III, n = 55; IV, n = 6. Extranodal manifestations were as follows: mediastinum, n = 28; lung, n = 13; skin, n = 16; soft tissue, n = 13; bone, n = 14; central nervous system, n = 1; bone marrow, n = 5. After a cytoreductive prephase, treatment was stratified into 3 branches: patients in K1 (stage I and II resected) received three 5-day courses (methotrexate [MTX] 0.5 g/m(2), dexamethasone, oxazaphorins, etoposide, cytarabine, doxorubicin, and intrathecal therapy); patients in K2 (stage II nonresected and stage III) received 6 courses; patients in K3 (stage IV or multifocal bone disease) received 6 intensified courses including MTX 5 g/m(2), high-dose cytarabine/etoposide. The Kaplan-Meier estimate for a 5-year event-free survival was 76% +/- 5% (median follow-up, 5.6 years) for all patients and 100%, 73% +/- 6%, and 79% +/- 11% for K1, K2, and K3, respectively. Events were as follows: progression during therapy, n = 2; progression or relapse after therapy, n = 20; second malignancy, n = 1. It was concluded that short-pulse chemotherapy, stratified according to stage, is effective treatment for pediatric ALCL. B symptoms were associated with increased risk of failure.

2. Prognostic factors in childhood anaplastic large cell lymphoma: results of a large European intergroup study.

Le Deley MC, Reiter A, Williams D, et al;

European Intergroup for Childhood Non-Hodgkin Lymphoma. Blood. 2008 Feb 1;111(3):1560-6.

To study prognostic factors of progression/relapse, data concerning 225 children enrolled between 1987 and 1997 in Berlin-Frankfurt-Münster, Société Française d'Oncologie Pédiatrique and United Kingdom Children's Cancer Study Group prospective studies for the treatment of anaplastic large cell lymphoma (ALCL) were merged. Median follow-up was 9.3 years. Five-year overall survival and event-free survival of the whole population was 81% (95% confidence interval, 76%-86%) and 69% (63%-74%), respectively. B symptoms, mediastinal involvement, skin lesions, visceral involvement, St Jude stage 3-4, Ann Arbor stage 3-4, and elevated lactate dehydrogenase increased the risk of progression/relapse in the univariate analysis. In the multivariate analysis, 3 factors remained significant: mediastinal involvement (relative risk [RR] = 2.1 [1.2-3.5]), visceral involvement defined as lung, liver, or spleen involvement (RR = 2.1 [1.3-3.6]), and skin lesions (RR = 1.9 [1.1-3.2]). Five-year progression-free survival (PFS) of the 81 patients with none of these risk factors was 89% [82%-96%], contrasting with a 5-year PFS of 61% [53%-69%] in the 144 patients with at least 1 risk factor (RR = 4.4 [2.2-8.9; P < .001). In conclusion, 3 factors associated with an increased risk of failure in childhood ALCL have been defined: mediastinal involvement, visceral involvement, and skin lesions.

3. Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: a report from the French Society of Pediatric Oncology.

Brugières L, Pacquement H, Le Deley MC, et al

J Clin Oncol. 2009 Oct 20;27(30):5056-61.

PURPOSE: To evaluate the efficacy of vinblastine for relapsed/refractory anaplastic large-cell lymphoma (ALCL).

PATIENTS AND METHODS: Data were reviewedon all 36 patients included prospectively in the French database for pediatric ALCL who were treated with vinblastine (6 mg/m(2)/wk) for resistant primary disease (one), a first relapse (15), or subsequent relapses (20). Fifteen patients had undergone hematopoietic stem-cell transplantation (HSCT) for a previous relapse.

RESULTS: Six patients were not evaluable for response, 25 (83%) of 30 evaluable patients achieved a complete remission (CR), and five experienced progressive disease. Among the 31 patients who achieved a CR with vinblastine or before its initiation, six patients were treated with HSCT and 25 with vinblastine alone (median duration, 14 months). Overall, nine of 25 patients treated with vinblastine alone have remained in CR (median, 7 years since the end of treatment), and 16 patients have relapsed. Vinblastine was still efficient for subsequent relapses. With a median follow-up of 9.2 years, 12 patients have died (four as a result of toxicity after HSCT and eight as a result of disease), and 24 patients are alive (15 following treatment with single-agent vinblastine for the last event). Five-year overall survival is 65% (95% CI, 48% to 79%), and 5-year event-free survival is 30% (95% CI, 17% to 47%).

CONCLUSION: Vinblastine is highly efficient in relapsed ALCL and may produce durable remissions. The optimal treatment duration still has to be assessed. These results should be borne in mind when designing future phase II

studies with the targeted therapies directed against anaplastic lymphoma kinase.

4. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group.

Brugières L, Le Deley MC, Rosolen A, et al.

J Clin Oncol. 2009 Feb 20;27(6):897-903.

PURPOSE: To compare the efficacy and safety of two methotrexate doses and administration schedules in children with anaplastic large-cell lymphoma (ALCL).

PATIENTS AND METHODS: This randomized trial for children with ALCL was based on the Non-Hodgkin's Lymphoma-Berlin-Frankfurt-Muenster 90 (NHL-BFM90) study protocol and compared six courses of methotrexate 1 g/m2 over 24 hours and an intrathecal injection (IT) followed by folinic acid rescue at 42 hours (MTX1 arm) with six courses of methotrexate 3 g/m2 over 3 hours followed by folinic acid rescue at 24 hours without IT (MTX3 arm). This trial involved most European pediatric/ lymphoma study groups and a Japanese group.

RESULTS: Overall, 352 patients (96% ALK positive) were recruited between 1999 and 2005; 175 were randomly assigned to the MTX1 arm, and 177 were assigned to the MTX3 arm. Ninety-two percent of patients received protocol treatment. Median follow-up time is 3.7 years. Event-free survival (EFS) curves were superimposed with 2-year EFS rates (73.6% and 74.5% in the MTX1 and MTX3 arms, respectively; hazard ratio = 0.98; 91.76%

CI, 0.69 to 1.38). Two-year overall survival rates were 90.1% and 94.9% in MTX1 and MTX3, respectively. Only two CNS relapses occurred (both in the MTX1 arm). Toxicity was assessed after 2,050 courses and included grade 4 hematologic toxicity after 79% and 64% of MTX1 and MTX3 courses, respectively ($P < .0001$); infection after 50% and 32% of courses, respectively ($P < .0001$); and grade 3 to 4 stomatitis after 21% and 6% of courses, respectively ($P < .0001$).

CONCLUSION: The results of the NHL-BFM90 study were reproduced in this large international trial. The methotrexate schedule of the NHL-BFM90 protocol including IT therapy can be safely replaced by a less toxic schedule of methotrexate 3 g/m2 in a 3-hour infusion without IT therapy.

Role of Hematopoietic Stem Cell Transplant in Paediatric Non Hodgkin lymphoma

With the development of well defined, risk adapted, intensive chemotherapy regimens in the current era, oncologists have been able to achieve a long term event free survival (EFS) of 80-90% in children with NHL. Though the above results are assuring, long term survival of children with relapsed or refractory lymphoma is poor, and well defined guidelines for this subgroup are in dearth. The current chapter will address the role of hematopoietic stem cell transplant (HSCT) in aggressive paediatric lymphomas.

We describe the role of SCT according to the histopathological subtypes of NHL.

I) SCT for mature B cell NHL

Patients with even advanced stage mature B- cell NHL have excellent disease free survival (DFS) rates of 80 – 90% with multi-agent fractionated chemotherapy. Most relapses tend to occur early during chemotherapy. Survival rates for children with salvage chemotherapy range from 10-20%. Though no randomised clinical trial

or meta-analysis comparing Auto-SCT and conventional chemotherapy for relapsed/refractory paediatric lymphomas are available, the evidence supporting the role of SCT is mainly from the retrospective reviews of various stem cell transplant registries and co-operative study groups.

The French Society of Paediatric Oncology (SFOP) reported in their study that all children with relapsed mature B- cell NHL who did not undergo SCT succumbed to their disease as compared to 3 year overall survival (OS) of 27% in those who underwent Auto-SCT. Later on, Ladenstein et al retrospectively analysed 89 children with poor risk Burkitt's lymphoma from European lymphoma registry who underwent Auto-SCT. Of these, 33 were in clinical remission (9 had poor initial response (PIR) to chemotherapy and 24 had relapse which responded to second line or third line chemotherapy, i.e. sensitive relapse) and 56 (28 had PIR and 28 had relapse i.e. were in partial remission) had evidence of disease at the time of transplant. Of the relapses, 38 had sensitive relapse and 14 had relapse resistant to chemotherapy. The 5 year EFS was 56.6 % for patients in partial remission (at least 50% response rate), 48.7% for patients with sensitive relapse. All patients with primary refractory disease and those with resistant relapse died in 1st year post SCT. Loiseau et al analysed 24 children with relapse and refractory NHL who underwent Auto-SCT. In this study authors found that only one out of seven children with refractory disease was a long term survivor.

Bureo et al in their retrospective analysis reported an EFS of 82.5% in a small group (n=13) of high-risk NHL patients with poor prognostic features (Partial or delayed

response to first line chemotherapy, central nervous system and bone marrow involvement at presentation) who were consolidated with high dose therapy followed by Auto-SCT in first complete remission (CR1). The authors concluded that, children with burkitt lymphoma having several poor prognostic features on presentation, as stated above may be considered for Auto-SCT in CR1 on an individual basis.

In relapsed setting, Auto-SCT has shown to improve outcome in patients who demonstrate PR to induction chemotherapy and patients with relapse sensitive to chemotherapy (Level III, Grade B). In addition, these data show that patients with primary refractory disease or chemo resistant relapse had no advantage from this aggressive procedure (Level IV, Grade C). It is difficult to deduct any recommendations from the small study by Bureo et al but a larger series may show benefit of upfront Auto-SCT in a selected group of high risk NHL patients. (Level of evidence: IV; grade of recommendation C).

Role of rituximab in SCT in B-NHL patients

In a further attempt to optimize conditioning regimens, there have been a few clinical trials of immunotherapy coupled with chemotherapy. Attias et al in their critical review revealed that paediatric relapsed and refractory Burkitt's/B-ALL and DLBCL, treated with rituximab alone or along with BFM 90 or BFM 95 show a response rate of 79% and a CR rate of 63%. This is vastly superior in comparison to published data which showed a salvage rate of 15% when relapsed B-cell lymphoma patients were treated on the Children's Cancer Group protocol (dexamethasone, high dose Ara-C, etoposide and cisplatin). Though the use of rituximab with standard

preparative regimens has been in few phase two trials of adult aggressive B-cell NHL, the data in paediatric setting is still lacking. The use of radio-labelled antibodies, 131 I-Tositumomab and 90 Yttrium-ibritumomab tiuxetan offers potential advantages over the unconjugated monoclonal antibodies in the setting of high dose chemotherapy and SCT but their use is restricted to phase I/II trials in adults.

We therefore conclude that, though the data for the use of rituximab as a part of salvage chemotherapy is encouraging, presently there is no evidence to recommend its use as a routine part of preparative regimens in paediatric stem cell transplantation. Larger paediatric studies are required to make rituximab a recommended addition to the preparative regimens in this population. Keeping in mind the significant established role of rituximab in upfront and relapsed B-cell NHL, it follows logically to expect the role of rituximab in SCT setting (Level IV, Grade C).

II) Stem cell transplant for Lymphoblastic lymphoma

Patients with relapsed lymphoblastic lymphoma (LL) have a worse survival when compared to relapsed B- cell NHL patients undergoing high dose chemotherapy and stem cell transplant. Won et al analysed 13 children with lymphoblastic lymphoma who underwent Auto-SCT and found a 2-year event-free survival (EFS) of 50.5 ±14.8%. Levine et al demonstrated that paediatric patients with relapsed LL had a 5 year survival of 39% following Auto-SCT. Sandlund et al from the St. Jude group transplanted four children with lymphoblastic lymphoma of which three were in relapse and one was having resistant disease. Of these, three died due to progressive disease post

transplant and one was in CR nine months post transplant. Loiseau et al from the French oncology group reported only one survivor out of eight children with lymphoblastic lymphoma who underwent Auto-SCT.

Since the results of autologous transplant are not encouraging in refractory and multiply-relapsed NHL, several clinical trials have tried allogenic transplant in a small series of children. The added advantage of graft versus leukaemia/lymphoma (GVL) effect, seen especially in children with lymphoblastic lymphoma comes at a cost of increased transplant related mortality (TRM) and graft versus host disease (GVHD). Gross et al in a recent study evaluated children less than 18 years with refractory or recurrent burkitt (n=36), lymphoblastic (n=53), DLBCL (n=52) and ALCL (n= 36), receiving Auto-SCT in 90 and Allo-SCT in 92 patients. Five-year EFS was similar after allogeneic and autologous HSCT for DLBCL (50% vs 52%), Burkitt (31% vs 27%), and anaplastic large cell lymphoma (46% vs 35%). However, EFS was higher for lymphoblastic lymphoma after allogeneic HSCT (40% vs 4%; P=.01). The above study also demonstrated that there was no difference in outcome by donor type used in Allo-SCT.

Levine et al reported the results from International Bone Marrow Transplant registry in 204 patients with LL following high-dose therapy and Auto-SCT (n= 128) vs Allo-SCT (n=76). Though, there was a similar DFS between Allo-SCT vs Auto-SCT in patients with LL (36 vs 39%) there was a significantly decreased risk of relapse following Allo-SCT at 1 and 5 years. Allo-SCT recipient had higher treatment related mortality (TRM) at 6months (18% versus 3%, P < .002).

As shown in the above data, the results of Auto-SCT in relapsed LL are variable and far from satisfactory (Level

III, Grade B). Auto-SCT could be recommended in those patients failing induction or with sensitive relapsed LL (Level IV, Grade C). Allo-SCT can be recommended for patients of refractory or relapsed LL with matched donor and in those who fail Auto-SCT (Level of evidence: IV; grade of recommendation B). Further studies are also required to fully elucidate the role of GVL effect.

III) Stem cell transplant for ALCL

The outcome for survival post SCT for children with chemosenstive relapse of ALCL is relatively favourable, when compared to B- cell NHL and LL. Fanin et al retrospectively analysed 64 adult and paediatric patients with T and null-cell $CD30^+$ ALCL who underwent Auto-SCT under EBMT registry. Out of 64 patients, all except one, transplanted in first CR (CR1), maintained the remission over time. Six of 15 transplanted in CR 2, six of 18 transplanted in PR (partial response was defined as more than 50% regression in the size of previous lesions after chemotherapy) and 14 of 16 transplanted in refractory disease (no response or less than 50% regression in the previous lesion) progressed. Actuarial overall survival (OS) at 10 years was 70%. Woessmann et al reported on the feasibility of intensive re-induction therapy followed by Auto-SCT or Allo-SCT in children and adolescents with relapsed ALCL after BFM front line therapy. The probability of OS at 3 years for $CD3^-$ vs $CD3^+$ patients was 62 and 46%, respectively. The relapse rate post Auto-SCT was signiûcantly higher in $CD3^+$ vs $CD3^-$ patients, 70% vs 9%; (P=0.001), respectively. The authors concluded that Auto-SCT is effective therapy for $CD3^-$ ALCL but not for $CD3^+$ tumours.

Brugieres et al from the SFOP group compared the results of salvage chemotherapy (carmustine,

vinblastine, bleomycin, Ara-c) in 15 children and stem cell transplant in 10 children with ALCL in CR 2. OS and DFS were 69% (53%-82%) and 44% (29%-61%) respectively at three years. In uni-variate analysis, patients treated with Auto-SCT while in CR2 did not appear to have a better outcome than the chemotherapy group. A long-lasting CR was obtained in 8 of 13 patients treated with weekly vinblastine for a relapse including 6 relapses occurring after Auto-SCT.

More recently, the BFM group reported the results in 20 children with relapsed or progressive ALCL following total body irradiation, cyclophosphamide and VP-16 followed by Allo-SCT, a DFS of 75% with a relapse rate of only 10% and TRM of 15% was reported. All five patients in this study who received Allo-SCT for relapse following Auto-SCT were in continuous CR.

The above data suggest that ALCL is an heterogeneous entity and though chemotherapy has a role in relapse setting, Auto-SCT can achieve a reasonable degree of OS and DFS in patients in CR-1 as well as in CR-2. (Level of evidence: IV; grade of recommendation C).

Conditioning regimes for SCT

Various conditioning regimens have been developed as alternatives to improve upon Auto-SCT results. To date, however, no comparative randomized trials have been performed and the optimal approach remains undetermined. Conditioning regimens used initially were based on total body irradiation (Cyclophosphamide -TBI), but now more commonly used regimens are BEAM (carmustine, etoposide, cytarabine, melphelan), Bu-Cy (Busulfan and cyclophosphamide), Bu-Cy-VP (Busulfan, cyclophosphamide and etoposide), CBV (Cyclophosphamide, carmustine and etoposide).

Conclusions

SCT has a definite role in most patients with relapsed/ refractory NHL. In relapsed setting, best results with Autologous SCT are achieved when the disease is chemo-sensitive and the response is complete or at least partial. In refractory NHL and chemo-resistant relapses Allogenic SCT may have a role. Allogenic SCT has been shown to have an outcome advantage over Autologous SCT in patients with relapsed lymphoblastic lymphoma and ALCL.

The future lies in finding individualized predictive and prognostic markers to optimally select patients for correct modality of treatment.

Suggested Reading

1. Ladenstein R, Pearce R, Hartmann O, et al: High-dose chemotherapy with autologous bone marrow rescue in children with poor-risk Burkitt's lymphoma: a report from the European Lymphoma Bone Marrow Transplantation Registry. Blood 90:2921-30, 1997

2. Bureo E, Ortega JJ, Munoz A, et al: Bone marrow transplantation in 46 pediatric patients with non-Hodgkin's lymphoma. Spanish Working Party for Bone Marrow Transplantation in Children. Bone Marrow Transplant 15:353-9, 1995

3. Won SC, Han JW, Kwon SY, et al: Autologous peripheral blood stem cell transplantation in children with non-Hodgkin's lymphoma: A report from the Korean society of pediatric hematology-oncology. Ann Hematol 85:787-94, 2006

4. Sandlund JT, Bowman L, Heslop HE, et al: Intensive chemotherapy with hematopoietic stem-cell support for children with recurrent or refractory NHL. Cytotherapy 4:253-8, 2002

5. Fanin R, Ruiz de Elvira MC, Sperotto A, et al: Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 23:437-42, 1999

6. Woessman W LM, Burkhardt B, Ebell W, Klingebiel T, Mann G etal.: Salvage strategy for anaplastic large cell lymphoma in children: prognostic impact of time to relapse and CD3 reactivity. Ann oncol 2005;16:(V62) Abstract 090.

Selected Abstracts

1. High-dose chemotherapy with autologous bone marrow rescue in children with poor-risk Burkitt's lymphoma: a report from the European Lymphoma Bone Marrow Transplantation Registry.

Ladenstein R, Pearce R, Hartmann O, et al.

Blood 90:2921-30, 1997.

To evaluate the role of high-dose chemotherapy (HDC) followed by Auto-SCT in children with poor-prognosis Burkitt's lymphoma, the European Lymphoma SCT registry was critically reviewed. Between February 1979 and July 1991, a selected group of 89 children (78 boys and 11 girls) were considered as Auto-SCT candidates in 12 European cancer centres for the following reasons:

poor initial response (PIR) to first-line chemotherapy in 28 patients, primary refractory disease (PRD) in nine patients, sensitive relapse (SR) in 38 patients, and resistant relapse (RR) in 14 patients. The median age at Auto-SCT was 8.2 years (range, 2.8 to 16.2 years). Thus, this report reflects data for patients surviving the salvage attempt deemed appropriate for HDC/Auto-SCT and who then actually underwent the transplant procedure. The median follow-up period after HDC/Auto-SCT was 4.3 years (range, 2 to 12 years). The prognosis was dismal for PRD patients and those with RR, i.e., all patients died within 1 year. The 5-year event-free survival (EFS) was 56.6% ($P < .0001$) for patients in partial remission (PR) and 48.7% ($P = .002$) for patients with SR. The toxic death rate was 11.1%. Continuous complete remissions (CRs) in 39.4% of these otherwise incurable children highlight the fact that HDC/Auto-SCT was an effective complementary procedure after conventional-dose chemotherapy protocols used during the given period. In addition, these data show that patients with PRD or RR clearly had no advantage from this aggressive and cost-intensive procedure. It has to be considered that the need for HDC/Auto-SCT has greatly diminished in parallel with the improvement in survival using the modern intensive pulsed CCT of current protocols. To further rescue patients failing to respond to modern protocols, new approaches appear necessary, i.e., combinations of HDC with antibody-targeted therapy plus allogeneic SCT for the additional benefits of the potential graft-versus-lymphoma effect.

2. High-dose chemotherapy containing busulfan followed by bone marrow transplantation in 24 children with refractory or relapsed non-Hodgkin's lymphoma.

Loiseau HA, Hartmann O, Valteau D, McDowell H, Brugières L, Vassal G, et al.

Bone Marrow Transplant. 1991 Dec;8(6):465-72.

Twenty-four children with relapsed or refractory non-Hodgkin's lymphoma underwent high-dose chemotherapy (HDC) with SCT. HDC comprised in all cases busulfan (16 mg/kg or 600 mg/m2), with either cyclophosphamide (200 mg/kg or 4.4 g/m2) and/or melphalan (140 mg/m2). Twenty-three of these children had received second-line therapy before receiving HDC. There were 16 B cell and eight T cell lymphomas. Twenty-three patients were evaluable at day 30 post-SCT; 19 were in complete remission, four did not respond. Eight patients are long-term survivors between 62 and 296 weeks after SCT. Among the seven children with resistant disease before HDC, only one is a long-term survivor. No toxic deaths occurred. The main adverse side effect was hepatic veno-occlusive disease which occurred in four patients, but resolved completely in all cases. Comparisons with other classic HDC regimens in relapsed childhood lymphomas show that HDC containing busulfan with SCT appears reasonably safe and is effective in refractory or relapsed lymphomas, even in these highly previously treated patients.

3. Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the European Group for Blood and Marrow Transplantation (EBMT).

Fanin R, Ruiz de Elvira MC, Sperotto A, et al:

Bone Marrow Transplant 23:437-42, 1999

Anaplastic large cell lymphoma (ALCL) is a

heterogeneous family of lymphoid tumours, among which the T and null cell types were recently listed in the REAL classification as a distinct entity. Reports on autologous stem cell transplantation (Auto-SCT) in this group are only occasional. Sixty-four patients with T and null cell ALCL from 25 European centres had been registered with the European Group for Blood and Marrow Transplantation (EBMT) at the onset of this study. The median age was 25 years (range 3.2-53.0). Thirty of the 64 patients (47%) were in complete remission (CR), 18 (28%) in partial remission (PR), and the remaining 16 (25%) had a more advanced or chemotherapy-refractory disease at transplant. Eighty-one percent of the patients were conditioned with chemotherapy alone and 75% received marrow stem cells. All the patients transplanted in first CR (15), except one, maintained the CR over time; six of 15 transplanted in CR subsequent to first, six of 18 transplanted in PR and 14 of 16 transplanted in refractory or relapsed disease progressed. Actuarial overall survival (OS) at 10 years is 70%. Multivariate analysis showed that good status at transplant, younger age, absence of B symptoms and absence of extranodal disease indicated a better prognosis. These data suggest that Auto-SCT should be considered as a possible treatment for chemo sensitive patients in CR or PR. However, definitive conclusions cannot be drawn from this study and a prospective randomised trial between Auto-SCT and conventional chemotherapy may be indicated.

4. Hematopoietic stem cell transplantation for refractory or recurrent non-hodgkin lymphoma in children and adolescents.

Gross TG, Hale GA, He W, et al:

Biol Blood Marrow Transplant, 2009

We examined the role of hematopoietic cell transplantation (HSCT) for patients aged </=18 years with refractory or recurrent Burkitt (n=41), lymphoblastic (n=53), diffuse large B cell (n=52) and anaplastic large cell lymphoma (n=36), receiving autologous (n=90) or allogeneic (n=92 - 43 matched sibling and 49 unrelated donor) HSCT in 1990-2005. Risk factors affecting event-free survival (EFS) were evaluated using stratified Cox regression. Characteristics of allogeneic and autologous HSCT recipients were similar. Allogeneic donor HSCT was more likely to use irradiation-containing conditioning regimens, marrow stem cells, be performed in more recent years, and for lymphoblastic lymphoma. EFS rates were lower for patients not in complete remission at HSCT, regardless of donor type. After adjusting for disease status, 5-year EFS were similar after allogeneic and autologous HSCT for diffuse large B cell (50% vs. 52%), Burkitt (31% vs. 27%) and anaplastic large cell lymphoma (46% vs. 35%). However, EFS was higher for lymphoblastic lymphoma, after allogeneic HSCT (40% vs. 4%, p<0.01). Predictors of EFS for progressive or recurrent disease after HSCT included disease status at HSCT and use of allogeneic donor for lymphoblastic lymphoma. These data were unable to demonstrate a difference in outcome by donor type for the other histologic sub-types.

Tata Memorial Hospital
Parel, Mumbai

ISBN 978-93-80251-03-5