

REVIEW

Current trends in large cell lymphoma

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For the last decade, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the best available standard of care for aggressive non-Hodgkin's lymphoma (NHL), based on equivalent therapeutic results with other multiagent chemotherapy accompanied by lower costs and lesser toxicity. However, only 40–45% of these patients are cured with CHOP. New treatment strategies have been employed, including the addition of Rituximab to CHOP in elderly patients; dose escalation using granulocyte-colony-stimulating factor; overcoming the multidrug resistance phenotype with infusional chemotherapeutic regimens and use of some newer agents. Furthermore, the International Prognostic Factor index (IPI) has permitted identification of subsets of patients with large variations in prognosis, allowing prognosis specific therapy to be tested. There is now accumulating evidence that the clinical behavior of certain NHL can be profiled by the expression of certain molecular markers, which will undoubtedly play a role in the development of new prognostic models that may refine our ability to identify poor-risk patients. Regardless, there is still significant opportunity for improving survival in large cell lymphomas.

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Introduction

Large cell non-Hodgkin's lymphoma (NHL) is primarily comprised of a number of different mature B- and T-cell NHL, as classified by the World Health Organization (WHO). The commonest among these is diffuse large B-cell lymphoma (DLBCL), which constitute 30–40% of adult NHL. There is a consensus that DLBCL represents a diverse group of neoplasms with heterogeneous genetic abnormalities, clinical features, treatment responses, and prognoses.¹ This article will focus primarily on this entity, attempting to review established as well as newer trends in its pathology, classification, prognosis, and treatment.

Pathology, biology, and classification of DLBCL

NHLs are heterogeneous lymphoproliferative malignancies, with different clinical behaviors and underlying biology. In contrast to many cancers whose incidence in the Western world is declining, the incidence of NHL is rising and is second only to melanoma in the rate of increase.

Historically, the NHLs were classified principally by morphologic features, primarily the presence or absence of a

follicular (nodular) pattern, and the size and shape of the malignant cells. However, by the early 1980s, with six major classification schemes in place there was difficulty in understanding which treatments were effective. In 1982, the results of a consensus classification were published as the Working Formulation (WF) (Table 1), which served as a uniform translation between existing classification schemes and divided all NHLs into three prognostic grades: low, intermediate, or high, based on the similarity of the survival curves of patients after therapy.² Many clinical investigators, especially in the United States, subsequently found it more convenient to divide NHL into two categories, indolent and aggressive. In this frame of reference, the indolent NHLs were WF categories A–E, and the remaining categories F–J were considered aggressive. Although the WF was easy to understand and used by the clinician, an ever-accumulating body of evidence indicated that many distinct diseases were being grouped together in this classification scheme.

In 1994, an international lymphoma study group proposed a 'revised' European–American lymphoma (REAL) classification encompassing all lymphoproliferative neoplasms, including NHL (Table 2). The REAL classification scheme defined 'real' disease entities, based on clinical and pathologic uniformity. The clinical significance and reproducibility of the proposed classification was confirmed in an international population-based study.³ Using the REAL classification, the entity reviewed in this article is termed DLBCL. The REAL classification of NHL and lymphoproliferative disorders has now been updated in the new WHO classification of hematopoietic and lymphoid tissues, a collaborative project of the European Association of Pathologists (EAP) and the Society for Hematopathology (SH).⁴

The WHO classification is more ambitious than the REAL and classifies all hematological malignancies, including lymphoid, myeloid, histiocytic, and mast cell neoplasms. The WHO approach to classification is based on the principle that a classification is a tabulation of 'real' disease entities, established by their morphology, immunophenotype, genetic features, and clinical features. A Clinical Advisory Committee (CAC) of international hematologists and oncologists was formed for the WHO organizers to ensure the classification would be suitable to clinicians. The recommendation of the CAC is that patient treatment be determined by the specific type of lymphoma, with supplementation of tumor grade, if applicable, and prognostic factors such as the International Prognostic Index (IPI).⁵ The final classification was published in 2001,⁶ which classified DLBCL as a mature B-cell neoplasm. Various morphologic variants and subtypes have been described (Table 3). They usually arise *de novo* (referred to as primary) but can represent progression/transformation (referred to as secondary) of a less aggressive lymphoma, for example, chronic lymphocytic leukemia, follicular lymphoma, marginal zone B-cell lymphoma, or nodular lymphocyte-predominant Hodgkin's lymphoma. Immunophenotypically, tumor cells generally express pan B-cell antigens

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(CD19, CD20, CD22, CD79a), as well as CD45 along with monoclonal surface membrane IgM; occasionally other heavy-chain isotypes are present. Uncommonly, DLBCL cells are CD10+, CD5+, or surface membrane immunoglobulin negative.^{7,8}

The morphologic variants described are centroblastic, immunoblastic, T-cell/histiocyte rich, and anaplastic. The immunoblastic variant requires clinical and/or immunophenotypic differentiation from extramedullary involvement by a plasmablastic variant of plasma cell myeloma. The T-cell-rich variant may need immunophenotypic differentiation from classical Hodgkin's lymphoma. Many cases of this variant were designated as diffuse mixed lymphoma in the WF. The anaplastic variant is biologically and clinically unrelated to

anaplastic large cell lymphoma of cytotoxic T-cell derivation. However, immunophenotypic and genetic parameters have not helped to delineate distinctive morphologic variants, and distinction among these variants has generally met with poor intraobserver and interobserver reproducibility.¹ The WHO classification also describes three subtypes of DLBCL that can be distinguished by their distinctive clinical features and/or immunophenotypic and genotypic features, that is, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma and primary effusion lymphoma (PEL). The former arises in the mediastinum, of putative thymic B-cell origin, presenting as a locally invasive anterior mediastinal mass with frequent airway compromise and superior vena cava syndrome.⁹ Although early studies suggested an unusually aggressive, incurable tumor, others have reported cure rates similar to those for other large cell lymphomas with aggressive therapy, usually combining chemotherapy with mediastinal irradiation.^{10–12} Intravascular large B-cell lymphoma is a rare subtype

Table 1 WF adapted from National Cancer Institute

Grade	International Working Formulation
Low grade	A. Small lymphocytic (SL) consistent with CLL B. Follicular (FSC) predominantly small cleaved cell diffuse areas C. Follicular mixed (FM) small cleaved and large cell
Intermediate grade	D. Follicular (FL) predominantly large cell E. Diffuse small cleaved cell (DSC) F. Diffuse mixed (DM) small cleaved and large cell G. Diffuse large cell (DL) cleaved or noncleaved cell
High grade	H. Immunoblastic large cell (IBL) I. Lymphoblastic (LL) convoluted or nonconvoluted cell J. Small noncleaved cell (SNC) Burkitt's or non-Burkitt's

Anonymous (*Cancer* 1982; **49**: 2112–2135).

Table 3 DLBCL, morphologic variants and subtypes

Morphologic variants	Subtypes
Centroblastic	Mediastinal (thymic) large B-cell lymphoma
Immunoblastic	Primary effusion lymphoma
T-cell/histiocyte rich	Intravascular large B-cell lymphoma
Lymphomatoid	
granulomatosis type	
Anaplastic large B cell	
Plasmablastic	

Adapted from Jaffe *et al.*⁴

Table 2 Real classification

B-cell neoplasms	T- and putative NK-cell neoplasms
<i>I. Precursor B-cell neoplasm</i> Precursor B-lymphoblastic leukemia/lymphoma	<i>I. Precursor T-cell neoplasm</i> Precursor T-lymphoblastic lymphoma/leukemia
<i>II. Peripheral B-cell neoplasms</i> A. B-cell CLL/PLL/small lymphocytic B. Lymphoplasmacytoid lymphoma/immunocytoma C. Mantle-cell lymphoma D. Follicle center cell lymphoma, follicular 1. Provisional cytologic grades: I (small cell), II (mixed small and large cell), III (large cell) 2. Provisional subtype: diffuse, predominantly small cell type E. Marginal zone B-cell lymphoma 1. Extranodal (MALT-type +/- monocytoid B cells) 2. Provisional subtype: nodal (+/- monocytoid B cells) F. Provisional entity: splenic marginal zone lymphoma (+/- villous lymphocytes) G. Hairy cell leukemia H. Plasmacytoma/plasma cell myeloma I. DLBCL 1. Subtype: primary mediastinal (thymic) B-cell lymphoma J. Burkitt's lymphoma K. Provisional entity: high-grade B-cell lymphoma, Burkitt like	<i>II. Peripheral T- and NK-cell neoplasms</i> A. T-cell CLL /PLL B. Large granular lymphocyte leukemia 1. T-cell type 2. NK-cell type C. Mycosis fungoides/ Sezary's syndrome D. Peripheral T-cell lymphomas, unspecified 1. Provisional cytologic categories: medium-sized cell, mixed medium and large cell, large cell, lymphoepithelioid cell 2. Provisional subtype: hepatosplenic gamma/delta T-cell lymphoma 3. Provisional subtype: subcutaneous panniculitic T-cell lymphoma E. Angioimmunoblastic T-cell lymphoma F. Angiocentric lymphoma G. Intestinal T-cell lymphoma (+/- enteropathy) H. Adult T-cell lymphoma/leukemia I. Anaplastic large cell lymphoma 1. CD30+ cell type 2. T-cell type 3. Null-cell types J. Provisional entity: anaplastic large cell lymphoma, Hodgkin's like

With permission from a revised European and American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group (*Blood* 1994; **84**: 1361–1392).

of extranodal DLBCL characterized by the presence of lymphoma cells only in the lumina of small vessels, particularly capillaries without an obvious extravascular tumor mass or leukemia.¹³ Owing to the nonspecific symptoms, the diagnosis is difficult, and many reported cases have been diagnosed only at autopsy. If a timely diagnosis is made and combination chemotherapy instituted, many patients achieve complete remission, and long-term survival appears to be possible.¹⁴ PEL is a neoplasm of large B cells usually presenting as serous pleural or peritoneal effusions without detectable tumor masses. It has a markedly aberrant phenotype, that is, absence of pan B-cell markers and lack of surface and cytoplasmic expression of Ig, often with the expression of activation and plasma cell-related markers (CD30, CD38, and CD138). This lymphoma is universally associated with human herpesvirus /Kaposi's sarcoma herpesvirus, most often occurring in the setting of immunosuppression. The clinical outlook is extremely unfavorable, with or without therapy, with a median survival of less than 6 months.⁶

Our understanding of the biology of DLBCLs is still in its infancy. Each of the categories of B-cell malignancy has been traced to a particular stage in normal B-cell development. It is axiomatic that some of the biology of a malignant cell is inherited from its normal cellular ancestors. Virtually all B-cell NHLs are derived from B-lineage cells that have completed both IgH and IgL recombination and can express functional Ig protein. Additionally, NHL can be divided into pregerminal center (pre-GC), germinal center (GC), and postgerminal center (post-GC) categories. The rearranged Ig genes in DLBCL bear mutations characteristic of somatic hypermutation, an antibody-diversification process that normally occurs within the GC of lymph nodes.¹⁵ Evidence suggests that DLBCL arises from B cells within the GC or at a later stage of differentiation (post-GC). Three recurring karyotypic abnormalities have been recognized in diffuse large-cell lymphomas: in approximately 30%, t(14;18) with *bcl-2* overexpression; in 30–40%, 3q27 rearrangements with *bcl-6* overexpression; and in some cases t(8;14) with *c-myc* overexpression. The proximity of these oncogenes to the Ig gene results in deregulation and increased expression of the gene product.

Bcl-2 belongs to a family of proteins regulating programmed cell death. Clues to *bcl-2* gene function came from transfection constructs and transgenic mice.^{16,17} Cells taken from *bcl-2* transgenic mice were found to survive long periods of time in culture without cell division, and thus *bcl-2* protein was found to prevent programmed cell death (apoptosis). Some *bcl-2* family members like *bcl-xL* have antiapoptotic roles, while others like *Bax* are proapoptotic. These proteins somehow respond to diverse forms of intracellular damage and combine these signals, by a mechanism that is incompletely understood, to decide an apoptotic outcome. A recent review updates the pro- and antiapoptotic *Bcl-2* family that are key in lymphoma pathogenesis, and expands on newly identified members of the *Bcl-2* family, such as *Bid* and *Bad*.¹⁸ Several studies have indicated that some of these molecular factors, such as increased expression of *Bcl-2*, are independent prognostic markers in diffuse large cell lymphomas.^{19,20}

Approximately 35% of diffuse large cell lymphomas demonstrate translocation of chromosome 3 band q27, the target of which has been termed *bcl-6*.²⁰ The product of the *Bcl-6* gene is a zinc-finger DNA-binding protein.²¹ *Bcl-6* represses transcription of target genes, which are yet to be elucidated.²² Translocations of 3q27 involve a variety of chromosome partners, including Ig loci on chromosomes 14, 2, and 22. In normal B cells, *Bcl-6* protein is found only in GCs. In fact, *Bcl-6*

may be required for GC formation, since no GCs form in *bcl-6* knockout mice.²³

The chromosomal translocation t(8;14) is characteristic of Burkitt's lymphoma, and is associated with the overexpression of *c-myc*, a member of the helix–loop–helix family of DNA-binding transcription factors. Diffuse large cell lymphomas rarely have t(8;14) detected. Overexpression of *c-myc* activates transcription and promotes cell division. Paradoxically, overexpression can induce apoptosis unless other mutations are present to inhibit apoptosis.²⁴ Mutations of *p53* occur commonly in solid tumors, but appear uncommon in lymphomas. Alterations in *p53* are more common in aggressive lymphomas and are associated with poor prognosis.^{25,26}

In 2000, Alizadeh *et al*²⁷ first reported on the application of the complementary DNA microarray techniques to DLBCL, which assess the expression level of thousands of genes by employing the mRNA extracted from frozen samples. In particular, they proposed that the diversity in gene expression among DLBCLs apparently reflected the variation in tumor proliferation rate, host response and differentiation state of the tumor, and that patients with a GC B-cell-like signature might run a more favorable course than those with an activated B-cell-like profile. The same group further strengthened their proposal by showing that GC B-cell-like DLBCLs (all associated with a good response to therapy) carried IgV_H gene ongoing mutations, CD10 expression and possibly t(14;18) – as expected in tumors of GC cells.²⁸ In January 2002, by adopting the oligonucleotide microarray strategy and a supervised learning prediction method, Shipp *et al*²⁹ showed that the outcome of patients with DLBCL, treated with CHOP-based chemotherapy, is influenced by gene-expression profiles other than the histogenetic ones. Genes of prognostic value seem to include some that regulate responses to B-receptor signaling, critical serine/threonine phosphorylation pathways and apoptosis. The model also delineated patients within specific IPI risk categories who were likely to be cured or to die of their disease. In June of 2002, Rosenwald *et al*³⁰ also demonstrated the favorable prognosis of GC B-cell-like diffuse large cell lymphoma. Biopsy samples of DLBCL from 240 patients were examined for gene expression with the use of DNA microarrays and analyzed for genomic abnormalities. They identified three subgroups with distinctive gene-expression profiles on the basis of hierarchical clustering: GC B-cell-like, activated B-cell-like, and type 3 DLBCL – were identified. Two common oncogenic events in DLBCL, *bcl-2* translocation and *c-rel* amplification, were detected only in the GC B-cell-like subgroup, which had the highest 5-year survival rate. Gene-expression profiling and tissue microarray have not only confirmed the heterogeneity of the DLBCLs, but for the first time provided criteria for its useful subclassification, by identifying groups of patients with different prognoses and different responses to the therapies at present available. Molecular genetics will no doubt be the next major impetus influencing the approach to lymphoma classification.

Best initial treatment for localized/limited stage DLBCL

NHL is usually staged by the Ann Arbor staging system.² Stage I disease is confined to a single lymph node region (I), or is a disease involving a single extralymphatic organ or site (IE). Stage II means involvement of two or more lymph node regions on the same side of the diaphragm, or involvement of an extralymphatic organ or site and its associated regional lymph nodes with or without other lymph node regions on the same side of the

diaphragm (IIE). Localized disease is commonly used in reference to stage I or II. Radiation therapy alone for localized DLBCL is an outmoded treatment.^{31,32} Initial disease control is good with involved field radiation; however, disease-free survival (DFS) at 5 years in patients treated only with involved field radiation is approximately 35%.³³ Several large phase II trials have consistently suggested that patients who received combined modality programs involving chemotherapy in addition to involved field radiation did significantly better than those who received radiation therapy alone.^{34–37} With the success of anthracycline containing combination chemotherapy in treating DLBCL, the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy with radiation therapy has emerged as the strategy of choice for treating localized DLBCL. Two randomized clinical trials have addressed the role of chemotherapy in localized aggressive NHL.^{38,39} The Southwest Oncology Group (SWOG) randomized 401 patients with nonbulky stage I or II DLBCL to three cycles of CHOP followed by involved field radiation or to eight cycles of CHOP alone.⁴⁰ The progression-free survival (PFS) and overall survival (OS) at 5 years were both significantly superior for the combined modality arm (PFS, 77 vs 64%: $P=0.03$; OS, 82 vs 72%: $P=0.02$). Overall life-threatening toxicity and cardiac toxicity were higher in the patients receiving CHOP alone (40 vs 30%: $P=0.06$). In the other randomized trial, the Eastern Cooperative Oncology Group (ECOG) randomized 210 patients who had attained CR after eight cycles of CHOP to no further therapy or involved field radiation. DFS at 6 years was superior for the combined treatment arm (73 vs 58%: $P=0.03$), but at 10 years, although the DFS ($P=0.05$) and time to progression ($P=0.06$) favored the combined modality treatment, there was no difference in OS ($P=0.24$).³⁹ In updates of both the above studies at the American Society of Hematology (ASH) meeting in 2001, factors predicting better or worse survival of patients with localized disease were analyzed. In the ECOG study, patients with three or more disease sites or a poor performance status were more likely to fail CHOP with or without radiation therapy.⁴¹ The SWOG study performed a subgroup analysis via a modified IPI, in which age >60 years, high LDH, stage II disease and performance status ≥ 1 were identified as poor-risk factors, 5-year OS was 94, 71, and 50% for those with no, one or three or more of these adverse risk factors, respectively.⁴⁰ They also demonstrated overlapping curves at 7 years for failure-free survival and at 9 years for OS. The treatment advantage for the combined modality arm seen for the first 7–9 years diminished because of excessive late relapses and deaths due to lymphoma occurring between years 5 and 10. Also, the OS for the entire group showed a continuous rate of death over the first 10 years with no evidence of plateau in the survival curve, a finding that was remarkably different from their previous experience in advanced stage disease using the same chemotherapy regimen.⁴² An early report from the Groupe d'Etudes des Lymphomes des l'Adulte (GELA) group in abstract form, in elderly patients with localized aggressive NHL and an age-adjusted IPI of zero has indicated that addition of involved field radiotherapy to four courses of CHOP did not improve rates of complete response (CR), 5-year EFS or 5-year OS, suggesting that four courses of CHOP chemotherapy alone may be sufficient in this highly selected population (Fillet G *et al. Blood* 2002; **100**: 92a; abstract). The authors recommend three cycles of CHOP with involved field radiation, as in the SWOG trial, for those with stage I and nonbulky stage II disease, based on survival advantages through the first 9 years and less associated toxicity. However, this approach appears to be less successful in those with bulky stage II disease, three or more

disease sites and/or a modified IPI score of three or more. This group appears to require more chemotherapy.

Best initial treatment for nonlocalized DLBCL

Before the development of multiagent chemotherapy, the median survival of patients with DLBCL was 1 year.⁵ The so-called 'first-generation' chemotherapy regimen, CHOP, has been studied extensively in randomized clinical trials, and has emerged as the current standard therapy for nonlocalized DLBCL. In trials, CHOP has repeatedly produced CR rates of 45–53%, with 30–37% long-term survivors.³² After CHOP was initially developed, 'second- and third-generation' lymphoma chemotherapy regimens were fashioned based on the concept of dose intensity, and were designed to deliver six to eight active lymphoma drugs at the highest possible drug dose per unit time. Single institution phase II trials of these second- and third-generation regimens demonstrated increased complete remission rates of 68–86% and survival rates of 58–69%, and these responses appeared superior to CHOP. However, a meta-analysis of five randomized controlled trials, involving over 1900 patients, failed to show any survival benefit of third-generation regimens over standard CHOP.⁴³ In a cooperative group setting, the ECOG conducted a randomized trial comparing CHOP to the second-generation m-BACOD (low-dose methotrexate with leukovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone), and found no difference in response or survival, but increased toxicity with m-BACOD.⁴⁴ That CHOP was equivalent to the newer regimens was conclusively demonstrated by Fisher *et al*⁴² in the SWOG trial 8516. This study was conducted in collaboration with the ECOG and compared standard therapy, CHOP, to the second- and third-generation chemotherapy regimens m-BACOD, ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leukovorin rescue), or MACOP-B (methotrexate with leukovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) in patients with stage II–IV disease, and working formulation intermediate- or high-grade lymphomas (D–H and J, excluding lymphoblastic lymphoma). After over 6 years, there is still no difference between CHOP and the newer regimens in PFS, with 5-year estimates of 33–38%, or in OS, with 5-year estimates of 45–46% (Figure 1 and 2). In this trial, patients received a maximum of eight cycles of CHOP. Although there are no randomized studies comparing the efficacy and toxicity of six vs eight cycles of CHOP, the former is used more commonly.

How could such disparate results occur between the single institution phase II studies and the subsequent national phase II, as well as the national phase III trials? One key explanation emerging is that DLBCL as identified in any of the current classification schemes, is not a uniform disease. Data supporting this concept are unambiguous and derive from recent studies on prognostic indices. The International Non-Hodgkin's Lymphoma Prognostic Factors Index (IPI) utilized pretreatment prognostic factors in a sample of over 5000 patients to develop a predictive model of outcome for DLBCL.³¹ The majority of patients had received adriamycin-based chemotherapy regimens. In an analysis of 2031 aggressive lymphoma patients (working formulation F, G, H) of all ages, five pretreatment characteristics were found to be independent predictors of death: age (<60 vs >60 years), tumor stage I or II (localized) vs III or IV (advanced), the number of extranodal sites of

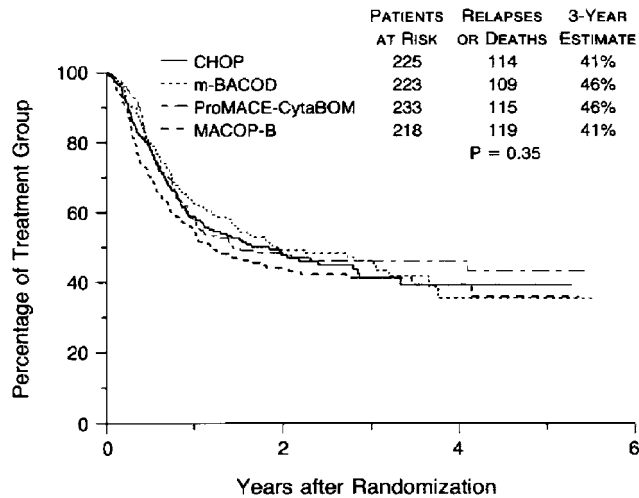


Figure 1 PFS by randomized treatment arm, with combination chemotherapies CHOP, m-BACOD, ProMACE-CytaBOM, and MACOP-B. Data from Fisher *et al* (*N Engl J Med* 1993; **328**: 1002–1006).

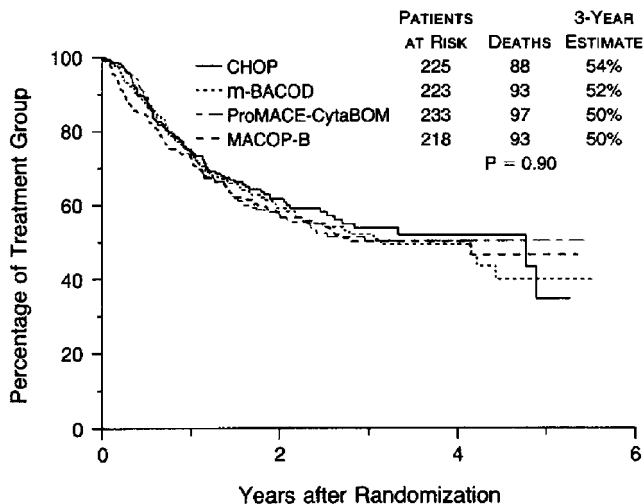


Figure 2 OS by randomized treatment arm, with combination chemotherapies CHOP, m-BACOD, ProMACE-CytaBOM, and MACOP-B. Data from Fisher *et al* (*N Engl J Med* 1993; **328**: 1002–1006).

involvement (<1 vs >1), patient ECOG performance status 0 or 1 (ambulatory) vs >2 (not ambulatory) (equivalent Karnofsky scores, greater than or equal to 80 and less than or equal to 70), and serum LDH level (less than or equal to 1 times normal vs >1 times normal). Each of the individual factors had comparable relative risks and thus could be summed together. The resulting model identified four risk groups with associated 5-year survival rates: low risk (0–1, risk factor) 73%; low intermediate risk (2, risk factors) 51%; high–intermediate risk (3 risk factors) 43%; and high risk (4–5 risk factors) 26% (Tables 4 and 5a, b). The increased risk of death was due to both a lower rate of complete responses and a higher rate of relapse from complete response. For example, patients in the high-risk IPI group had a CR rate of 44% and a 5-year survival rate of only 26% as compared to a CR rate of 87% and a 5-year survival of 73% in patients in the low-risk IPI group. The IPI has provided us with a methodology to compare the patients entering various clinical trials, and explained the variation in treatment outcomes

Table 4 IPI (patients of all ages)

Risk group	Risk factors ^a	Frequency (%)	CR rate (%)	2-year survival (%)	5-year survival (%)
Low	0.1	35	87	84	73
Low–intermediate	2	27	67	66	51
High–intermediate	3	22	55	54	43
High	4.5	16	44	34	26

From Anonymous (*N Engl J Med* 1993; **329**: 987–994).

^aScore 0 or 1 for each factor. 0 = absent, 1 = present.

initially attributed to the effect of ‘third-generation’ chemotherapy. The percent of patients with favorable (low) IPI scores in the National Cancer Institute original trial of ProMACE-CytaBOM (44%) was almost twice that in the subsequent SWOG-8516 phase III study (22%).^{44,45} The differences in outcome caused by these imbalances in patient prognostic factors can easily exceed any treatment differences between the actual therapies. It is important to remember that these clinical factors are proxy measures for the underlying biologic and molecular variation within the large cell lymphoma disease category. The recent molecular studies, using gene-expression profiling, described above are even more convincing testimony to the heterogeneity of DLBCLs. The role of monoclonal antibody (mAb) therapy in this group of patients is discussed later in the paper.

Therapy for high–intermediate and high-risk IPI group DLBCL patients

Current therapy with CHOP is unsatisfactory for patients with DLBCL in high–intermediate- or high-risk IPI categories, with 54 and 34% 2 year survivals, respectively, indicating that the majority of these patients have little chance of cure with conventional chemotherapy. However, the current status of our lack of knowledge in this group of patients provides no uniform answer to a therapy of choice in this situation. Controlled clinical trials if available to the physician, are the best option for patients in these risk groups. Some of the current treatment options being investigated are the use of high-dose chemotherapy (HDT) with stem cell rescue, and chemotherapy combined with mAbs and or radioimmunotherapy.

Treatment with HDT

Rationale for testing high-dose therapy with stem cell support in previously untreated patients with aggressive NHL was provided by the results of the PARMA trial in relapsed NHL.^{46,47} In this study, patients less than age 60 years who had relapsed after an initial complete remission and were without evidence of central nervous system disease or bone marrow involvement were first treated with two courses of conventional DHAP salvage chemotherapy. Those patients responding with a CR or PR were then considered to be chemosensitive and were randomized to involve field radiotherapy and high-dose BEAC chemotherapy with autologous BMT vs DHAP chemotherapy for four cycles followed by involved field radiotherapy. The EFS of patients randomized to high-dose therapy was 46% compared to 12% for patients receiving salvage chemotherapy alone ($P=0.001$) and the OS was also superior in the high-dose therapy group ($P=0.038$) (Figure 3 and 4). This study defined high-dose

Table 5 (a) Age adjusted IPI (patients ≤ 60 years) and (b) prognostic risk factors

Risk group	Risk factors ^a	Frequency (%)	CR rate (%)	2-year survival (%)	5-year survival (%)
(a)					
Low	0	22	92	90	83
Low-intermediate	1	32	78	79	69
High-intermediate	2	32	57	59	46
High	3	14	46	37	32
(b)					
Patients of all ages (years)	Patients age ≤ 60 years				
Age > 60 years					
LDH > normal	LDH > normal				
Performance status ≥ 2	Performance status ≥ 2				
Ann Arbor stage III or IV	Ann Arbor stage III or IV				
Extranodal involvement > 1 site ^b					

Anonymous (*N Engl J Med* 1993; **329**: 987–994).

^aScore 0 or 1 for each factor. 0 = absent, 1 = present.

^bThis was the only factor that did not retain independent significance in patients < 60 years.

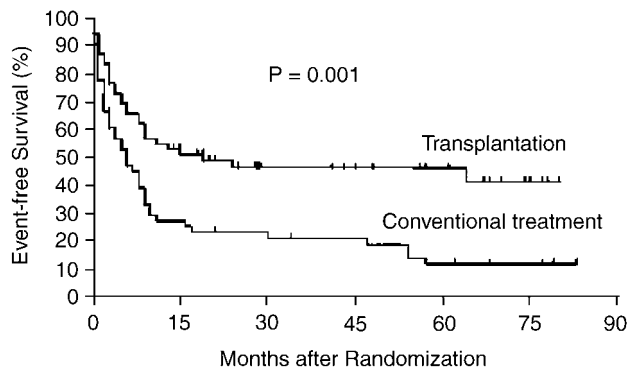


Figure 3 EFS, by intention-to-treat analysis, of patients treated in the PARMA trial with HDT and autologous transplantation and conventional DHAP therapy. Data from Philip *et al* (*N Engl J Med* 1995; **333**: 1540–1545).

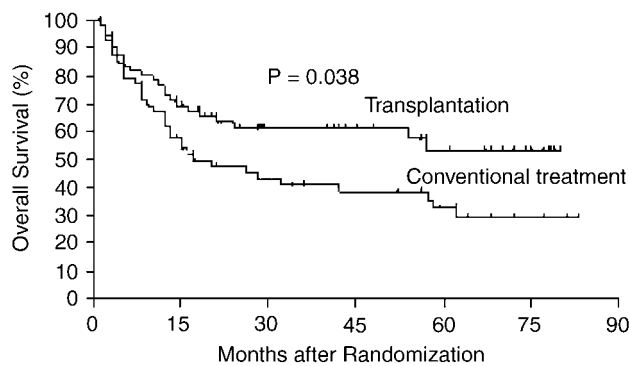


Figure 4 OS, by intention-to-treat analysis, of patients treated in the PARMA trial with HDT and autologous transplantation and conventional DHAP therapy. Data from Philip, T. *et al* (*N Engl J Med* 1995; **333**: 1540–1545).

therapy in previously untreated patients would prove to be beneficial.

HDT with stem cell support as consolidation after CR, or as induction therapy, has been tested in newly diagnosed untreated DLBCL patients in several phase II^{48–52} and phase III^{53–59} trials. Phase II studies suggested a possible benefit for HDT in poor-risk patients unlikely to be cured by conventional strategies. The results from these studies formed the basis for several randomized phase III studies that investigated the benefit of upfront HDT for poor-risk individuals. In the majority of these trials, poor-risk disease was identified by criteria other than the IPI or age-adjusted IPI. Various paradigms for upfront HDT were investigated, namely, following a CR after a full course of induction therapy;^{53,55} following a CR or PR⁵⁷ or ‘minor’ response⁶⁰ after abbreviated standard-dose chemotherapy or abbreviated dose-intense chemotherapy;^{56,59,61} and following a ‘slow’ response to induction chemotherapy⁵⁴ (Table 5 and 6).

The most mature data in support of the use of HDT in high-risk group DLBCL patients come from the final report of the LNH87-2 trial of the GELA.⁵⁵ In this trial, 1043 patients were enrolled at 35 participating centers from October 1987 to February 1993. Patients included were less than 55 years old with newly diagnosed intermediate- or high-grade NHL according to the International Working Formulation and with at least one of the following adverse factors: ECOG performance status of 2–4, two or more extranodal sites, tumor burden of at least 10 cm in largest dimension, bone marrow or CNS involvement, and Burkitt’s or lymphoblastic subtypes (the latter two without bone marrow or CNS involvement). Patients were initially randomized to treatment with four courses of either of two anthracycline containing regimens (ACVB or NCVB), and then all received the same four additional courses of cyclophosphamide 1200 mg/m² given intravenously on day 1, vindesine 2 mg/m² given intravenously on days 1 and 5, bleomycin 10 mg given intravenously on days 1 and 5, prednisone 60 mg/m² given orally on days 1–5, and intrathecal methotrexate 15 mg on day 2. The study tested HDT as consolidation, and patients achieving a CR were randomized to additional cycles of sequential chemotherapy or HDT with CBV (cyclophosphamide, carmustine, and etoposide) and autologous stem cell transplant (ASCT). In the initial analysis reported for all study patients, there were no treatment-related differences in the

therapy with stem cell support as the treatment of choice for relapsed aggressive lymphomas for patients that met the other eligibility criteria of the Parma study. In addition, this study also raised the question of whether the earlier use of high-dose

Table 6 A summary of recent phase II and III trials of high-dose chemotherapy for newly diagnosed poor prognosis DLBCL

Study	Phase	N	Induction chemotherapy	Use of HDT	Outcome
Gulati <i>et al</i> ⁴⁹	II	31	Multiple regimens	Consolidation	Improved DFS with HDT
Freedman <i>et al</i> ⁵⁰	II	26	Multiple regimens	Consolidation	Improved DFS with HDT
Pettengell <i>et al</i> ⁵¹	II	33	VAPEC-B ^a	Consolidation	Improved DFS with HDT
Nademanee <i>et al</i> ⁴⁸	II	42	Multiple regimens	Consolidation	Improved DFS with HDT
Cortelazzo <i>et al</i> ⁵²	II	44	MACOP-B ^b	Consolidation	Improved DFS with HDT
Verdonck <i>et al</i> ⁵⁴	III		CHOP ^c	Consolidation	No difference overall in EFS and OS
Santini <i>et al</i> ⁵⁷	III	124	VACOP-B ^d in all	Consolidation	No difference overall in DFS/PFS (high IPI subset: improved DFS with HDT)
Gianni <i>et al</i> ⁵⁶	III	98	HDT v. MACOP-B ^b	Initial treatment	Improved DFS with HDT
Kluin-Nelemans <i>et al</i> ⁵⁸	III	194	CHVmP/BV ^e	Consolidation	No difference overall in DFS or in high-risk IPI subset
Haïoun 2000 <i>et al</i> ⁷⁰	III	236	ACVB ^f or NCVB ^g w/ sequential chemotherapy	Consolidation	Improved DFS and OS with HDT
Gisselbrecht <i>et al</i> ⁵⁹	III	370	ACVBP ^h w/sequential chemotherapy	Initial treatment	Inferior DFS and OS with HDT

^aDoxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide, prednisolone, and methotrexate.

^bMethotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

^cCyclophosphamide, doxorubicin, vincristine, and prednisone.

^dEtoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

^eCyclophosphamide, doxorubicin, teniposide, and prednisone, with bleomycin and vincristine added at mid-cycle.

^fDoxorubicin, cyclophosphamide, vinblastine, and bleomycin.

^gMitoxantrone, cyclophosphamide, vinblastine, and bleomycin.

^hDoxorubicin, cyclophosphamide, vinblastine, bleomycin, and prednisone.

3-year OS or DFS.⁵³ However, this trial was instituted before the publication of the IPI, and treatment-related differences became apparent when study patients were retrospectively grouped into risk groups according to the age-adjusted IPI. In the retrospective analysis, 451 patients were determined to be high–intermediate- or high-risk IPI patients (two risk factors, $n=318$; three risk factors, $n=133$), and 277 (61%) achieved CR and were eligible for the randomization to HDT or chemotherapy. However, 41 patients (14.8%) were not randomized, and the analysis presented by the authors was of the 236 randomized patients: 125 patients in the HDT arm and 111 in the sequential chemotherapy arm. In the final LNH87-2 report,⁵⁵ HDT as consolidation was found superior to sequential chemotherapy, with an 8-year DFS of 55% (95% CI, 46–64%) in the HDT arm, and 39% (95% CI, 30–48%) in the sequential chemotherapy arm ($P=0.02$; relative risk, 1.51). The 8-year OS was also superior in the HDT arm at 64% (95% CI, 55–73%) compared with the sequential chemotherapy arm 49% (95% CI, 39–59%) ($P=0.04$; relative risk, 1.56). However, this trial was not analyzed as intention to treat, and nearly 15% of the eligible patients did not receive the consolidation therapy. Moreover, it is not known if the unusual induction ACVB therapy used in this trial, instead of the more standard CHOP chemotherapy, affected the outcome. ACVB appears more toxic than CHOP, as indicated by data from the LNH87-1 trial that showed greater toxicity for ACVB when compared to m-BACOD.⁶² Prior studies have shown greater toxicity of m-BACOD compared to CHOP.⁴² Subgroup retrospective analyses have also demonstrated that patients with high–intermediate- and high-risk disease by the age-adjusted IPI did appear to benefit from upfront HDT, when administered after a full course of standard chemotherapy,⁵⁷ regardless of response and following abbreviated dose-intense therapy.⁵⁶ Prior to accepting these results consideration should be given to the fact that for most of these phase III trials reported to date, the high-risk patients were not initially identified as the target population for the trial, and

subset analysis and retrospective assignment of IPI risk groups were common to these studies.

Additional concerns about the use of HDT arise when induction chemotherapy courses are shortened, as in the LNH93-3 trial⁵⁹ and that conducted by Gherlinzoni *et al*.⁶¹ The latter is a multicenter randomized trial comparing conventional chemotherapy (MACOP-B) to early ASCT as front-line treatment for NHL patients with at least two risk factors according to age-adjusted IPI. A total of 150 patients were enrolled into the trial, with 75 randomized to receive MACOP-B for 12 weeks, while the other 75 were randomized to receive MACOP-B for 8 weeks (mini-MACOP-B), followed by ASCT, using BAVC (BCNU, cytarabine, etoposide, cyclophosphamide) as HDT. In the HDT arm, 30 out of 75 (40%) did not undergo ASCT for several reasons, the most frequent being early disease progression during the interval between mini-MACOP-B and ASCT. No differences were observed in terms of PFS or relapse-free survival (RFS) on an intention-to-treat analysis. Similar results were seen in the LNH93-3 trial.⁵⁹ Patients under 60 years of age with high IPI risk factors were randomized between conventional ACVB followed by sequential consolidation and an experimental intensified induction phase rescued by peripheral blood stem cells (PBSC). The intensified induction consisted of three cycles of chemotherapy, and granulocyte-colony-stimulating factor (G-CSF) was used to collect PBSC after cycle two or three. On day 60, a BEAM regimen (BCNU 300 mg/m², etoposide 200 mg/m² × 4 days, Ara-C 200 mg/m² × 4 days, and melphalan 140 mg/m²) was administered followed by stem cell rescue. A total of 370 patients were randomized, and CR rates were similar in both arms. Of the patients, 26% did not receive the BEAM regimen mainly due to early progression. With a median follow-up of 60 months, 5-year EFS and OS were inferior in the HDT arm. These data suggest that feasibility is a major problem of early HDT and that early intensification with ASCT is not superior to conventional chemotherapy.

Several recent reviews and a consensus of experts highlight the fact that the role of HDT as primary therapy in high-risk NHL patients is not yet defined, and conclusions should await additional randomized phase III trials.^{63–65} Chief among concerns for its use as upfront therapy in NHL is the long-term toxicity of HDT. A recent report from the Dana-Farber Cancer Institute describes the incidence of myelodysplastic syndrome (MDS) after autologous BMT.⁶⁶ All patients in this study were treated with a uniform regimen, and 41/552 developed MDS at a median of 47 months after ABMT for NHL. The incidence of MDS was 7.4%, and the actuarial incidence at 10 years was 19.8%. Most concerning was the lack of evidence of a plateau. With the exception of LNH87-2, the majority of the current mature phase III trials report improved DFS, but not OS with HDT in patients under age 60 years, who are in high IPI risk groups, but not lower risk groups. The data support the hypothesis that high–intermediate- and high-risk patients with aggressive lymphoma who receive full course standard induction therapy will benefit from the addition of high-dose therapy. Based on this hypothesis, a United States intergroup trial is underway to compare early vs delayed high-dose therapy for patients with high–intermediate- and high-risk large cell NHL. Patients who achieve a CR or PR after five cycles of CHOP are randomly assigned to receive three more cycles of CHOP or one more cycle of CHOP followed by HDT. This trial should determine whether upfront transplantation for poor-prognosis patients confers a benefit when used to ‘consolidate’ a response achieved with primary therapy.

Treatment with mAbs

In one of the most intensively investigated areas in lymphoma therapy, combinations of mAbs and chemotherapy are now being explored for DLBCL treatment. One of the most important developments in antibody-based therapy of malignant lymphomas has been the generation of chimeric mAbs, exemplified by the chimeric anti-CD20 antibody (IDEC-C2B8, Rituximab, Rituxan™, IDEC Pharmaceuticals, CA, USA). This construct consists of murine mAb 2B8 heavy- and light-chain variable regions of the antigen-binding site for the CD20 antigen, and the human Fc IgG1-κ constant region. This chimeric antibody is 1000-fold more potent in the activation of human complement and interaction with human effector lymphocytes (ADCC, antibody-dependent cellular toxicity) compared with the unmodified murine mAb.⁶⁷ In addition to the activation of complement and ADCC, a portion of the tumoricidal effect of this antibody is attributable to other mechanisms. For example, the antibody is highly efficient in inducing apoptotic death in B-NHL cell lines *in vitro*.^{68,69} While most of the initial studies with this mAb focused on the indolent lymphomas, Coiffier *et al*⁷⁰ have reported an overall response rate of 37% in relapsing or refractory aggressive lymphoma patients when treated with Rituximab as a single agent. Winkler *et al*⁷¹ reported similar results with Rituximab alone, achieving two CR and two PR (21% RR) in 19 patients with primary or transformed DLBCL. Thus, although responses with Rituximab alone are seen in relapsed or primary DLBCL, CRs are rare.

Rituximab has been combined with CHOP chemotherapy in the treatment of newly diagnosed indolent NHL with few added toxicities, and with the intriguing finding of molecular remissions as defined by clearance of BCL-2 by PCR.⁷² Expanding this concept, Vose *et al*⁷³ have reported a phase II study of Rituximab plus CHOP in untreated DLBCL. In the initial report of this study, the overall response rate was an impressive 97% (32/33), with 20 CR and 12 PR.

Since the older NHL patient has decreased CR rates, shorter DFS, and is generally not eligible for the HDT trials described above, the use of Rituximab combined with CHOP chemotherapy is also being explored in an intergroup trial for older patients. In this study, patients 60 years of age or greater with DLBCL have been randomized between CHOP and CHOP plus Rituximab (four doses given at day -3, -7, 41, 83). Results from the initial analysis of this study are expected fairly soon. The GELA has published the results of a randomized trial in this setting. Elderly patients (median age 69 years, range: 60–80 years) with previously untreated advanced DLBCL were randomly assigned to receive either eight courses of standard dose CHOP given every 3 weeks or to the same regimen plus the monoclonal anti-CD20 antibody Rituximab (375 mg/m²) on day 1 of each of the eight cycles of CHOP (CHOP-R). Complete response rates of 63 and 76% ($P=0.005$) and 2-year OSs of 57 and 70% (relative risk for CHOP-R vs CHOP: 0.64, $P=0.007$) were achieved by CHOP and CHOP-R, respectively (Figure 5 and 6). The incidence of severe or serious side effects was similar in the two treatment arms.⁷⁴

In patients with a low-risk age-adjusted IPI (0 or 1 adverse prognostic factors), 1-year EFS was 81 and 57% for the CHOP-R and CHOP arms, respectively ($P<0.001$). For those with high-risk disease (two or three adverse factors), median EFS was 18 and 10 months for the CHOP-R and CHOP arms, respectively ($P=0.01$). (Coiffier *et al. Proc Am Soc Clin Oncol* 2001; **20**: 283a; abstract) These results suggest that addition of Rituximab therapy to standard CHOP may lead to significant prolongation of EFS and OS in elderly patients with both high- and low-risk disease with no increase in toxicity. In an early analysis, CHOP-R appeared to be more effective than CHOP in bcl-2-positive, but not in bcl-2-negative, patients, suggesting that the addition of Rituximab might overcome bcl-2 associated chemotherapy resistance.⁷⁵

Additional mAbs and antibody conjugates have been less well studied in DLBCL patients compared to Rituximab. Epratuzumab (hLL2, LymphoCide™), a humanized mAb-directed against the B-cell CD22 antigen, was studied in a phase I/II trial as a single agent in a group of 24 patients with refractory or relapsed DLBCL, 47% having had prior Rituximab therapy.⁷⁶ In 17 evaluable patients, two CRs (11%) and three PRs (18%) were

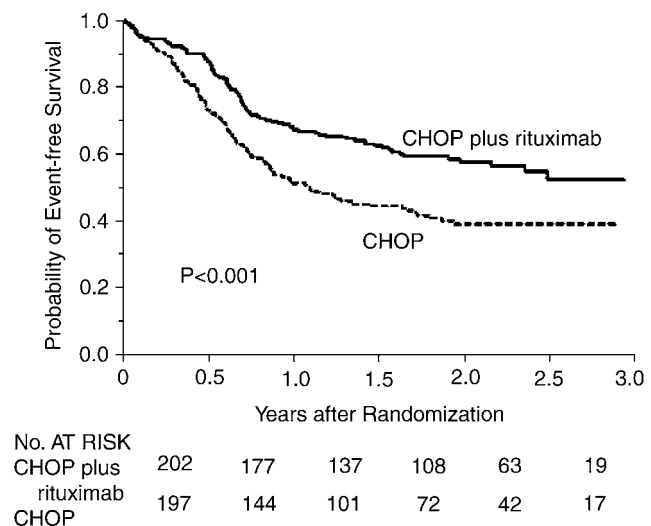


Figure 5 EFS among 399 patients assigned to chemotherapy with CHOP or with CHOP plus Rituximab. Data from Coiffier *et al*.⁷⁴

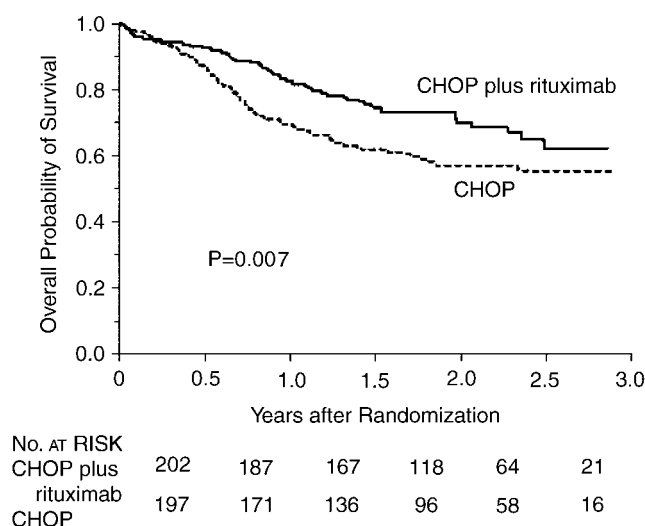


Figure 6 OS among 399 patients assigned to chemotherapy with CHOP or with CHOP plus Rituximab. Data from Coiffier *et al.*⁷⁴

observed. This antibody is also being developed as a radio-immunoconjugate to be studied in patients with various NHL.⁷⁷ Other radioimmunoconjugates have also been reported in the treatment of DLBCL in phase I/II studies. Lym-1, a mAb labeled with iodine 131 (¹³¹I), was studied in 21 patients with advanced NHL with mixed histologies, and 13 (62%) of these patients had DLBCL.⁷⁸ All these patients had disease resistant to standard therapy and had received a mean of four chemotherapy regimens. The overall response was 11 (52%) of 21 total patients, while in 14 patients who received at least two doses of ¹³¹I-Lym-1 therapy, 10 (71%) responded. Seven of these responses were complete, with a mean DFS duration of 14 months. Another agent, Tositumomab, is a mouse Ig G2a (IgG2a) mAb specific for CD20, which has been combined with ¹³¹I (Tositumomab, BexxarTM) for lymphoma therapy.⁷⁹ Dr Kaminski *et al.*⁸⁰ reported long-term data on 59 chemotherapy treated relapsed/refractory NHL patients who were treated in their phase I/II single-center trials between 1990 and 1996 with ¹³¹I Tositumomab. Of the 42 patients with low-grade or transformed NHL, 35 (83%) responded, while seven (41%) of 17 with *de novo* intermediate-grade NHL responded. Overall 42/59 (71%) patients responded, with 20 (34%) achieving CR and a median PFS of 20.3 months in the CR patients. Another radioimmunoconjugate has also been tested in NHL, IDEC-Y2B8 (ibrutumomab tiuxetan, ZevalinTM, IDEC Pharmaceuticals Corp.). IDEC-Y2B8 is composed of a murine IgG- κ monoclonal antibody ibritumomab (IDEC-2B8); the linker tiuxetan; and the radioisotope Yttrium-90 (⁹⁰Y). Like its unlabeled chimeric counterpart, Rituximab, IDEC-Y2B8 targets the CD20 antigen. In all, 51 patients with relapsed or refractory low-grade or follicular B-cell NHL and patients with intermediate-grade and mantle-cell NHL in first or subsequent relapse were treated in a phase I/II trial.⁸¹ The overall response rate for the intent-to-treat population ($n=51$) was 67% with 26% CR. In this study, 82% overall response (26% CR) was seen in low-grade disease ($n=34$), and 43% overall response for intermediate-grade disease ($n=14$), while for mantle-cell NHL ($n=3$), 0% responses were seen. Thus, at least two unconjugated mAbs are currently in clinical trials for DLBCL, one targeting the CD20 antigen, and the other CD22, and with active investigation of mAb-chemotherapy combinations proceeding. Radioimmunoconjugates with different isotopes are also under investigation in

DLBCL, and these agents may offer an increase in response over unlabeled monoclonal antibody when used as a single agent in relapsed or refractory DLBCL.

New agents

The discovery of new drugs for the treatment of large cell lymphoma remains difficult. The large number of active agents already in use, as well as the high number of complete remissions seen in untreated patients, means that a drug must have outstanding single agent activity in phase II testing before it is considered for evaluation as a front-line agent. Drugs that would be considered promising in some solid tumors are discarded as marginally active in the lymphomas. In addition, many patients who are not cured by initial therapy are now considered for high-dose salvage therapy at first relapse. Thus, the pool of patients available for phase II testing now consists of patients ineligible for high dose therapy or those relapsing after that treatment.

Nevertheless, some new agents now are under investigation, including aminocamptothecin (9-AC), irinotecan (CPT-11), gemcitabine and arsenic trioxide (As₂O₃). 9-AC is a topoisomerase I (topo I)-targeting agent. In a preliminary report, 9-AC demonstrated an overall response rate of 10/40 (25%) in heavily pretreated relapsed and refractory lymphoma patients, with chemotherapy-sensitive patients showing a 32% response rate.⁸² CPT-11, another topo I inhibitor, has a board range of antitumor activity⁸³ and reports of its activity in lymphoma have been reported in a phase II trial,⁸⁴ in which patients with relapsed or refractory NHL, treated with CPT-11, demonstrated an overall response rate of 38% (12 of 32 evaluable patients) in the entire cohort. Specifically, 44% of the 18 relapsed aggressive NHLs and 20% of the five refractory aggressive NHLs responded. A phase II evaluation sponsored by the NCI is also underway. CPT-11, in combinations with other agents^{85,86} have also been evaluated. Gemcitabine has also demonstrated clinical activity in relapsed or refractory aggressive NHLs.^{87,88} As₂O₃ is an active agent in patients with acute promyelocytic leukemia, and can induce clinical remissions via induction of differentiation and programmed cell death. *In vitro* studies indicate substantial growth inhibition and apoptosis without

differentiation in fresh lymphoma tumor cell lines after exposure to clinical levels of As₂O₃.⁸⁹ A novel agent, PS-341, a proteasome inhibitor, is in phase I trial for lymphomas and refractory tumors. The ubiquitin-proteasome pathway plays a critical role in the regulated degradation of proteins involved in cell cycle control and tumor growth, and interruption of this pathway by agents such as PS-341 cause cells to undergo apoptosis.⁹⁰ At present, there are no drugs demonstrating unequivocally high levels of single agent activity in the diffuse large cell lymphomas.

CSF for dose escalation

CSFs have allowed several groups to double the dose intensity of marrow toxic drugs such as cyclophosphamide, doxorubicin and etoposide. Shipp *et al*⁹¹ reported encouraging pilot data using G-CSF to dose escalate cyclophosphamide to 4 gm/m² and doxorubicin to 70 mg/m² in a CHOP-like regimen. The Cancer and Acute Leukemia Group B (CALGB) subsequently tested dose escalation of cyclophosphamide and etoposide in the CHOPE regimen using G-CSF with no benefit in the overall survival compared to standard dose CHOP.⁹² SWOG has completed a randomized phase II study of dose intensified CHOP and dose intensified ProMACE-CytaBOM with G-CSF support.⁹³ This trial has demonstrated possible survival benefit of the former in comparison to historical controls. The ECOG has reported a successful phase I dose-escalation study of ProMACE-CytaBOM and subsequently completed a phase II study of that regimen. Longer-term follow-up is required before the results of these studies can be evaluated.

Reversing drug resistance

Since pleiotropic drug resistance develops in a significant number of NHL patients, SWOG has conducted phase II studies with infusional CHOP plus verapamil and quinine aimed at preventing the emergence of this resistance factor. To date increased bone marrow toxicity has been demonstrated, but there is no improvement in RFS compared to historical controls treated with CHOP. Quinine and verapamil are first-generation MDR inhibitors and newer, more potent inhibitors of drug resistance such as PSC-388 and similar agents are currently in early clinical trials.

Role of allogeneic stem cell transplantation

The role of allogeneic transplantation in the management of patients with relapsed or primary refractory aggressive NHL has been difficult to discern from earlier studies because of the small number of patients, the inclusion of patients with various histologies, and the lack of homogeneity with respect to chemosensitivity. Whereas some studies have suggested that patients with indolent NHL have a better outcome after allogeneic transplantation compared with patients with an aggressive histology,^{94,95} other studies have suggested that the reverse is true.⁹⁶ Many studies have demonstrated that chemosensitive disease predicts for a better outcome.^{97,98,99,96,100,101} Very few studies have compared the outcome of allogeneic transplantation with that of autologous transplantation for NHL, none of which have been prospective randomized trials. Whereas some studies revealed that patients undergoing allogeneic transplantation had lower relapse

rates^{98,99} as compared to those undergoing autologous transplantation, others demonstrated that the type of transplant did not influence either relapse rate or DFS.¹⁰² However, none of the studies showed an improvement in OS with allogeneic transplantation and a report from the European Bone Marrow Transplant lymphoma registry demonstrated an inferior survival in patients that underwent allogeneic transplantation.¹⁰² The lack of a survival benefit is due to the high procedure-related mortality associated with allogeneic transplantation, which can range from 30 to 40% for patients with aggressive NHL.^{98,103} Nonmyeloablative allogeneic transplantation is being explored currently as a means to harness the potentially powerful graft-versus-lymphoma effect, while minimizing the mortality associated with traditional allogeneic transplantation. Its role in the treatment of patients with relapsed or primary refractory aggressive NHL remains to be determined.

Conclusions and future directions

Prospective randomized clinical trials are only successful when they are based on positive leads provided by solid phase II trials. However, the application of this concept is not always straightforward. In the past, many of the promising phase II studies in DLBCL have appeared beneficial based on patient selection bias and not the therapeutic result. The prognostic factor index now allows us to evaluate the expected therapeutic results based on the mixture of patient risk categories. CHOP has remained the standard treatment for diffuse large cell lymphomas for over 20 years, but its benefit is limited. It is time to improve. Multiple rationale strategies are now being explored. Improved application of mAb therapy in combination with CHOP may advance therapy. Continued investigation of HDT in relapsed and primary refractory disease may further our treatment of this condition. Progress in the application of nonmyeloablative stem cell transplant in high-risk IPI for relapsed and primary refractory disease may yield benefit for this poor-prognosis category. As our understanding of the molecular biology of NHL improves, and our ability to manipulate genes translates from the bench to the clinic, molecular targets will become the focus of many therapeutic trials. Thoughtful clinical investigation is the key to future progress in NHL.

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