

Treatment strategies for patients with diffuse large B-cell lymphoma: past, present, and future

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Abstract: Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring lymphoma in the Western world. DLBCLs are clinically, biologically, and pathologically heterogeneous with biologically distinct subtypes that have different expected treatment outcomes. The addition of rituximab to combination chemotherapy has improved outcomes for all patients with DLBCL and can cure the disease in certain individuals. Relapsed DLBCL is generally managed with salvage chemoimmunotherapy followed by high-dose therapy and autologous stem cell transplantation, which can cure additional patients. However, outcomes for patients who relapse early after upfront rituximab and chemotherapy are poor. Novel therapies and strategies are desperately needed for these patients and several emerging treatments hold promise for improving DLBCL treatment outcomes.

Keywords: non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, lymphoma, chemoimmunotherapy, rituximab, treatment

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma (NHL) in the Western world, accounting for about one-third of all lymphomas in adults. DLBCL is aggressive, with untreated patients having a median survival of <1 year. The incidence of NHL increased dramatically from the 1970s to the mid-1990s, with an estimated 66,360 new cases diagnosed in the USA in 2011.¹ The 3%–4% per year increase in the number of cases of lymphoma and DLBCL occurred in both genders, across racial categories, and across all age groups except the very young.^{2–4} A number of factors may have contributed to the increased incidence, including more sensitive methods for diagnosing new cases, improvements in cancer reporting for hematological malignancies, changes in the classification systems used for lymphoid malignancies, and the rise in human immunodeficiency virus-associated DLBCL.⁵ However, these factors account for approximately 50% of the additional cases⁶ and the cause of the remaining increase in DLBCL is unclear.

Patients are typically in their seventies when diagnosed with DLBCL, although there do appear to be racial differences in the age of onset for DLBCL and other NHLs, with African Americans typically presenting at a younger age.^{2,4,7} Patients with DLBCL commonly present with a rapidly enlarging, painless lymph node. However, in up to 40% of patients, the first site involved is extranodal. Approximately 15% of patients present with bone marrow involvement, approximately one-third have B-symptoms (fever, night sweats, and weight loss), nearly half have stage III/IV disease using the Ann Arbor staging system, and more than

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half have elevated serum lactate dehydrogenase (LDH).⁶ Patients diagnosed with DLBCL need to undergo full staging work-up, which helps determine the treatment schedule, identify prognostic information, and predict the likelihood of survival.

Originally proposed in 1993, the international prognostic index (IPI) remains the primary clinical tool used to predict outcome for patients with DLBCL.⁸ The five factors in the IPI score include stage III/IV disease, elevated LDH, age >60 years, an Eastern Cooperative Oncology Group performance status of 2 or more, and involvement of more than one extranodal site. Each factor scores one point, and the total allows patients to be stratified into four discrete groups: (1) low risk, (2) low intermediate risk, (3) high intermediate risk, and (5) high risk, with a 5-year overall survival (OS) ranging from 26% to 73%. For patients with IPI scores of 0–1, 2, 3, and 4–5 points, the 5-year OS is 73%, 51%, 43%, and 26%, respectively. This model also serves as a tool for clinical trial design and interpretation. However, the IPI was developed prior to the era of rituximab. The revised IPI published by Sehn et al defines three separate outcome categories.⁹ Among patients treated with rituximab-containing regimens, those with zero risk factors had >90% chance of 4-year progression-free survival (PFS), those with 1–2 risk factors have approximately 80% expected PFS, and those with three or more risk factors have approximately 50% PFS. However, this system was not prospectively evaluated, so the original IPI method remains the best validated prognostic approach.

Pathophysiology

As its name implies, DLBCL is a cancer of large B-cells that most commonly grows in a diffuse pattern completely effacing the normal lymph node architecture.¹⁰ Given that DLBCLs are clinically, biologically, and pathologically heterogeneous, the 2008 World Health Organization classification system established several modifications to DLBCL classification to recognize variants based on improved understanding of the molecular and genetic abnormalities associated with DLBCL.^{11,12} Growing knowledge of DLBCL biology has led to the recognition that DLBCL is mostly composed of at least two biologically distinct pathophysiologic entities. DLBCL can be classified by gene-expression profiling into the germinal center B-cell (GCB) subtype and the activated B-cell (ABC) subtype, which is derived from different cells of origin.^{13,15} The Lymphoma/Leukemia Molecular

Profiling Project reported approximately 60% GCB and 40% non-GCB subtypes in newly diagnosed DLBCL biopsy samples that were examined by gene expression.^{14,15} Immunohistochemistry (IHC) assessment of CD10, BCL-6, MUM1, and other markers has been developed as a simpler counterpart to gene-expression profiling to classify cases of DLBCL into GCB and non-GCB (including ABC and other subtypes) using an assay that is more widely amenable to routine hematopathology practice.¹⁶

Researchers from a range of countries have employed the Hans algorithm to segregate subcategories of DLBCL. Alacacioglu et al evaluated 50 Turkish patients and found that 30% were GCB and 70% were non-GCB.¹⁷ Saad et al inspected blocks from a retrospective series of 30 patients from Ain Shams University Hospital and National Cancer Institute, Cairo, Egypt, and determined that 57% were GCB and 43% were non-GCB.¹⁸ Fu et al classified 131 patients from the Nebraska Lymphoma Study Group and determined that 52% were GCB and 48% were non-GCB.¹⁴ In Japan, Castillo et al analyzed data from 730 patients and determined that 48.2% were GCB and 51.8% were non-GCB¹⁹ and Yamauchi et al analyzed 81 young patients with DLBCL and found that of 50 classified patients, 41% were GCB and 59% were non-GCB.²⁰ Shiozawa et al evaluated 248 Japanese patients, of whom 29% had GCB and 71% had non-GCB DLBCL.²¹ Thus, there appear to be racial and/or regional differences in the frequency of DLBCL subtypes.

While a consensus on the specific markers, techniques, and algorithms to use during IHC to distinguish GCB versus non-GCB subtypes has not yet been reached, a positive predictive value of 73% to 87% for IHC compared with gene-expression profiling has been reported based on CD10, BCL-6, and MUM1 IHC assays.¹⁶ Meyer et al recently examined published algorithms using IHC data to replicate microarray results.²² The authors proposed implementation of the Tally algorithm, as it was the most predictive of gene-expression profiling while maintaining prognostic relevance and feasibility. The Tally algorithm scores two antigens of GCB (CD10 and GCET1) and two antigens of ABC (MUM1 and FoxP1) in no particular order and allots a score of 1 if expressed in more than 30% of cells, so allowing the immunophenotype with more positive antigens to be determined. If the score is equal, the GCB antigen LMO2 serves as a tiebreaker. In this study, the Choi algorithm and the Hans algorithm had high concordance with the gene-expression profiling results (87% and 86%, respectively), but the Tally method achieved 93% concordance and produced GCB and

ABC subgroups that were significantly different in terms of event-free survival (EFS) and OS among DLBCL patients treated with rituximab-containing regimens.

Treatment

Limited-stage disease

Limited-stage disease usually includes Ann Arbor stage I and non-bulky stage II disease and can be more clearly defined as disease contained within one irradiation field. Thirty to forty percent of patients with DLBCL present with limited-stage disease. Those patients presenting with bulky stage II disease (ie, mass >10 cm) have similar outcomes to stage III and IV disease and are therefore treated as advanced-stage disease.²³ Most patients with non-bulky limited-stage DLBCL are treated with combined modality therapy consisting of systemic chemotherapy (ie, 2–4 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]) with rituximab, followed by loco-regional radiation therapy (Table 1). The benefit of rituximab in this patient population was clearly shown in the randomized MabTherapy International trial, which demonstrated an OS benefit with the addition of rituximab to CHOP-like chemotherapy.²⁴ Four trials have compared chemotherapy followed by radiation therapy versus chemotherapy alone for patients with limited-stage lymphoma.^{25–27,29,30} All these trials were conducted in the era prior to rituximab and their conclusions were highly variable, allowing for continued debate about the most appropriate treatment for patients with limited-stage disease.

The SWOG 8736 trial randomly assigned 401 patients to treatment with either eight cycles of chemotherapy or three cycles of CHOP followed by 40–55 Gy of involved field radiation therapy (IFRT).²⁵ At a median follow-up of 4.4 years, the radiation arm had higher rates of 5-year PFS

(77% vs 64%) and OS (82% vs 72%). However, data reported in abstract form show that there were no differences in failure-free survival and OS between the two treatment arms.²⁶ This was largely due to late relapses and lymphoma deaths after 5 years in patients who received abbreviated chemotherapy followed by radiation therapy (RT). These findings suggest that three cycles of CHOP is an inadequate systemic therapy, despite the fact that this trial included a relatively favorable group of patients – half of the patients were younger than 60 years, two-thirds of the patients had stage I disease, and patients with bulky stage II disease were excluded.

A similar study in patients with low risk stage I–II aggressive NHL, in which 81% of patients had DLBCL, the Groupe d'Etude des Lymphomas de l'Adulte (GELA) LNH 93-1 trial, compared aggressive chemotherapy alone to abbreviated chemotherapy followed by radiation therapy. A total of 647 patients were randomized to three cycles of CHOP followed by IFRT or dose-intensified ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) followed by sequential consolidation without RT.²⁷ Patients in this trial were <61 years of age, had normal LDH levels and performance statuses, and two thirds had stage I disease. Although the addition of RT after three cycles of CHOP reduced relapses at initial sites of the disease, it was not enough to overcome the excessive distant relapses after the abbreviated therapy. Patients randomly assigned to receive ACVBP, which had a theoretical dose-intensity of at least 150% of that delivered by three cycles of CHOP, had significantly higher 5-year event-free and OS rates. Although data on sites of relapse were not provided, it may be surmised that most of the treatment failures under CHOP plus RT were at distant sites of disease outside the RT field. One conclusion of this trial may be that the micrometastatic tumor burden in

Table 1 Summary of clinical trials for the treatment of localized diffuse large B-cell lymphoma

Trial sample size	Regimen (s)	Overall response rate	Survival comparison	Reference
SWOG 8736 (n = 401)	CHOP × 3 + IF-XRT vs CHOP × 8	ORR 75% vs 73%	EFS 76% vs 67% (<i>P</i> = 0.003) OS 82% vs 74% (<i>P</i> = 0.02)	25, 26
GELA LNH 93-1 (n = 647)	ACVBP × 6 vs CHOP × 3 + IF-XRT	ORR 95% vs 93%	EFS 82% vs 74% (<i>P</i> < 0.001) OS 90% vs 81% (<i>P</i> = 0.001)	27
ECOG 1484 (n = 353)	CHOP × 8 + IF-XRT vs CHOP × 8	Not reported	EFS 69% vs 53% OS 87% vs 73	29
GELA LNH 93-4 (n = 576)	CHOP × 4 + IF-XRT vs CHOP × 4	ORR 91% vs 92%	EFS, 61% vs 64% OS 72% vs 68%	30
SWOG 0014 (n = 60)	R-CHOP × 3 + IF-XRT vs historical controls	Not recorded	EFS 88% vs 78% OS 92% vs 88%	31

Abbreviations: ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; GELA, Groupe d'Etude des Lymphomas de l'Adulte; IF-XRT, involved-field radiation therapy; ORR, overall response rate; OS, overall survival; R-CHOP, rituximab in combination with CHOP; SWOG, Southwest Oncology Group.

patients with bulky stage II disease is too high to be eradicated by three cycles of CHOP, and patients could be better served if they received treatment designed for advanced disease. In another trial of ACVBP there were increases in secondary myelodysplasia/acute myelogenous leukemia and lung cancer among men,²⁸ so this more aggressive regimen may not be ideal for young patients with limited stage disease.

In the Eastern Cooperative Oncology Group 1484 trial, 172 patients with stage I or II aggressive lymphoma in complete response (CR) after eight cycles of CHOP were randomly assigned to receive 30 Gy IFRT or simply be observed. Patients assigned to IFRT had a significantly higher rate of disease-free survival (69% vs 53%) and a trend toward better 5-year OS (87% vs 73%).²⁹ Elsewhere, the GELA LNH 93-4 trial reported on patients aged >60 years with localized aggressive lymphoma and normal LDH levels and performance statuses.³⁰ Two-thirds of the patients had stage I disease and 8% had bulky disease. Patients were randomly assigned at diagnosis to four cycles of CHOP alone or four cycles of CHOP followed by RT to 40 Gy. Although the final number of patients was slightly lower than the target accrual, the recruitment of 574 patients gave this trial an 85% power to detect a 10% EFS difference. Patient and disease characteristics were well balanced in the two arms and a central review of the technical details of the radiation therapy was conducted. At a median follow-up of 7 years, there were no significant differences in 5-year EFS (61% vs 64% for chemotherapy alone and combined-modality therapy, respectively) and OS (72% vs 68%) between the two arms.

There have been no definitive randomized trials comparing chemoimmunotherapy to radiation therapy since the introduction of rituximab, but a study has compared rituximab with CHOP followed by IFRT to historical controls.³¹ In SWOG 0014, 60 patients with newly diagnosed aggressive, CD20-expressing NHL were treated with four doses of rituximab (infused on days -7, 1, 22, and 43) and CHOP (administered on days 3, 24, and 45), followed 3 weeks later by 40–46 Gy of IFRT. Patients had limited-stage disease and at least one adverse risk factor as defined by the stage-modified IPI (non-bulky stage II disease, age greater than 60 years, World Health Organization performance status of 2, or elevated serum LDH). With the median follow-up of 5.3 years, treatment resulted in a PFS of 93% at 2 years and 88% at 4 years. OS was 95% at 2 years and 92% at 4 years. These results were compared with those from the historical group of patients treated without rituximab on SWOG 8736, demonstrating PFS of 78% and OS of 88% at 4 years. Taken together, these trials demonstrate that abbreviated

chemotherapy plus IFRT is at least as effective as a full course of the same chemotherapy regimen and may be associated with a lower rate of relapse at local sites of disease in the first years of follow-up. However, the later results of SWOG 8736 need to be considered before discarding the potential role for more cycles of therapy. In the future, imaging-directed response-adapted therapy may aid in determining which patients are likely to benefit most from radiation.^{32,33}

Advanced-stage disease

For the majority of patients, DLBCL is a systemic disease at the time of diagnosis. At the completion of the initial staging evaluation, bulky stage II, stage III, or stage IV disease is documented in approximately 75% of all DLBCL patients. Therefore, chemotherapy has been the critical component of treatment. Although the standard chemotherapy regimen has not significantly changed over the past three decades, the incorporation of monoclonal antibody therapy into the standard treatment program represents an improvement in OS for the majority of patients with DLBCL (Table 2). CHOP was known to cure approximately 30% of patients with advanced stages of intermediate-grade or high-grade NHL.^{34,35} Single-arm studies suggested that more complex regimens such as low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD); prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM); and methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) had improved efficacy to CHOP. However, follow-up was short and these new treatment regimens were more difficult to administer, more toxic, and more costly.^{36–38}

Therefore, in 1986, a US intergroup prospective randomized Phase III trial was initiated.³⁴ Each treatment group contained at least 218 patients. There were no significant differences among the groups in the rates of partial response (PR) and CR. At 3 years, 44% of all patients were alive without disease; there were no significant differences between the groups (41% in the CHOP and MACOP-B groups and 46% in the m-BACOD and ProMACE-CytaBOM groups; $P = 0.35$). OS at 3 years was 52% (50% in the ProMACE-CytaBOM and MACOP-B groups, 52% in the m-BACOD group, and 54% in the CHOP group; $P = 0.90$). Fatal toxic reactions were less common in patients treated with CHOP, establishing this regimen as the standard of care for patients with DLBCL. This finding has been confirmed by other

Table 2 Summary of key clinical trials for the treatment of advanced stage diffuse large B-cell lymphoma

Trial sample size	Regimen (s)	Overall response rate	Survival comparison	Reference
SWOG/ECOG (n = 899)	CHOP vs MACOP-B vs m-BACOD vs ProMACE- CytaBOM groups	80 % CHOP; 82% m-BACOD; 83% MACOP-B and 87% ProMACE-CytaBOM	3-year OS 50% ProMACE- CytaBOM and the MACOP-B groups, 52% m-BACOD group, 54% CHOP	34
GELA LNH 98.5 (n=399)	R-CHOP vs CHOP	CR/CRu – 76% vs 65%	5-year OS 58% R-CHOP vs 45% CHOP	45, 46
ECOG 4494 (n = 632) Responders (n = 415)	R-CHOP vs CHOP Responders: Maintenance R vs observation	ORR 77% vs 76%	3-year FFS 53% R-CHOP and 46% CHOP 3-year OS 67% R-CHOP and 58% CHOP	74
MInT (n = 823)	R-CHOP vs CHOP	CR/CRu – 86% vs 68%	3-year OS 93% for RCHOP vs 84% for CHOP	24
Cunningham (n = 1080)	R-CHOP 21 × 8 vs R-CHOP 14 × 8	ORR 88% vs 99%	OS at 2 years was 81% for R-CHOP21 and 83% for R-CHOP14 arm.	48
GELA LNH 03-6B (n = 202)	R-CHOP 21 × 8 vs R-CHOP 14 × 8	OR 84% for RCHOP 21 vs 81% for RCHOP 14	OS at 2 years was 70% for RCHOP21 and 67% for RCHOP14	49
GELA LNH 03-2B (n = 380)	R-ACVBP vs R-CHOP	ORR was 90.3% in the R-ACVBP group and 88.5% in the R-CHOP group (P = 0.57)	OS at 3 years was 92.2% for R-ACVBP vs 83.8%	51

Abbreviations: ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CRu, complete response undetermined; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; GELA, Groupe d'Etude des Lymphomas de l'Adulte; IF-XRT, involved-field radiation therapy; LNH, non-Hodgkin's lymphoma; MACOP-B, methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; m-BACOD, methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; MInT, MabTherapy International trial; ORR, overall response rate; OS, overall survival; ProMACE-CytaBOM, prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue; R, rituximab; R-ACVBP, rituximab in combination with ACVBP; R-CHOP, rituximab in combination with CHOP; SWOG, Southwest Oncology Group.

trials comparing more aggressive chemotherapy regimens to standard CHOP therapy.³⁹⁻⁴¹

Nearly a decade later, rituximab was approved for follicular lymphoma and was soon applied to DLBCL. Rituximab is thought to induce lymphoma cell lysis through different immunologic or direct mechanisms, complement-mediated cytotoxicity, antibody-dependent cell cytotoxicity, and induction of apoptosis, and acts synergistically with chemotherapy.⁴²⁻⁴⁴ On the basis of Phase II studies in which rituximab in combination with CHOP had a good safety profile and induced response rates in more than 90% of patients with indolent and aggressive lymphoma, GELA undertook a study to compare CHOP plus rituximab with CHOP alone in patients aged >60 years with DLBCL. The CR rate was significantly higher in patients receiving CHOP plus rituximab than in those who received CHOP alone (76% vs 63%, $P = 0.0005$). After a median follow-up of 2 years, the OS was higher in the rituximab in combination with CHOP (R-CHOP) group.⁴⁵ Longer follow-up of this trial have demonstrated that EFS, PFS, and OS remained statistically significantly in favor of the R-CHOP combination and outcomes actually continued to improve.⁴⁶

In an attempt to improve on the results seen with CHOP-21 (CHOP administered every 21 days), trials have investigated the use of more dose-intense chemotherapy. The most popular of these regimens is CHOP-14, which is given every 14 days with growth factor support. In a related trial by Economopoulos et al, patients were treated with cyclophosphamide, epirubicin, vincristine (Oncovin®), and prednisone (CEOP) every 2 weeks (CEOP-14) or every 3 weeks (the standard CEOP-21 regimen).⁴⁷ After 2002, rituximab was added to the regimen and therefore the trial examined the impact of adding rituximab to CEOP-14/CEOP-21 chemotherapy. The study reported similar response rates and survival between the two groups; however, the addition of rituximab to both the 14- and 21-day regimens improved on OS and time to progression. Further research continues to compare dose-intense chemotherapy to the standard with the addition of rituximab.

More recently, Cunningham et al compared R-CHOP-14 with R-CHOP-21 in a Phase III study of 1080 newly diagnosed DLBCL patients.⁴⁸ Patients were randomly assigned to a group that received eight cycles of standard R-CHOP-21 or six cycles of R-CHOP-14 with two additional cycles

of single-agent rituximab. All patients on R-CHOP-14 received G-CSF prophylaxis. There were more grade 3/4 neutropenia (77% vs 37%)⁴⁸ and febrile neutropenia (11% vs 5%) in the R-CHOP-21 arm whereas there were more thrombocytopenia (5% vs 9%) and anemia (1% vs 3%) with R-CHOP-14. Grade 3/4 non-hematologic toxicity included infection (25% R-CHOP-21 vs 19% R-CHOP-14), cardiac complications (<1% R-CHOP-21 vs 2.6% R-CHOP-14), and neurological issues (8% R-CHOP-21 vs 11% R-CHOP-14). Overall response rates were similar between the two arms [63% CR or complete response undetermined (CRu) on R-CHOP-21, and 58% on R-CHOP-14 ($P = 0.15$)]. With a median follow-up of 39 months, failure-free survival and OS (81% for R-CHOP-21 and 83% for R-CHOP-14) were identical. Subgroup analysis did not identify any subgroup that benefited from R-CHOP-14.

Delarue et al presented the results of the planned interim analysis of the LNH03-6B, a multicenter, Phase III open-label, randomized trial comparing the efficacy of R-CHOP-14 and R-CHOP-21.⁴⁹ A total of 202 patients with a median age of 72 years were randomized and 201 received study treatments (103 with R-CHOP-14 and 98 with R-CHOP-21). Patients' characteristics were similar in both groups with a slightly higher proportion of patients with an age-adjusted international prognostic index (aaIPI) score of 2–3 in the R-CHOP-14 arm (67% vs 59%) whereas a higher proportion of patients in the R-CHOP-21 arm presented with B symptoms (43% vs 37%). Seventy-three patients (71%) in the R-CHOP-14 group and 74 patients (76%) in the R-CHOP-21 group completed eight cycles without progression. Overall response rates at 2 years including PFS (49% in RCHOP-14 vs 63% in RCHOP-21) and OS (67% vs 70%) were similar in both groups. Grade 3–4 hematological toxicity was more frequent in the R-CHOP-14 group, with a higher proportion of patients receiving red cell or platelet transfusions and/or experiencing febrile neutropenia, resulting in a higher proportion of patients hospitalized for adverse events. The results of this interim analysis of the LNH03-6B trial and other trials favor treatment with R-CHOP-21 in elderly patients with DLBCL, and showed trends toward higher efficacy and lower toxicity of R-CHOP-21 compared with R-CHOP-14.

Two trials conducted in the pre-rituximab era showed the superiority of the intensive chemotherapy regimen ACVBP over standard CHOP in DLBCL.^{27,50} To investigate the role of intensive chemotherapy associated with rituximab, GELA initiated a multicenter Phase III open-label randomized trial in 2003 to compare the efficacy and safety of R-ACVBP

versus R-CHOP in younger DLBCL patients with an aaIPI of 1. Compared with R-CHOP-21, R-ACVBP resulted in a similar CR rate (83% vs 80%), and superior 3-year EFS (81% vs 67%) and OS (92% vs 84%) rates.⁵¹ A follow-up subgroup analysis of the LNH 03-2B trial suggests that the survival benefit related to R-ACVBP over R-CHOP is in large part due to a survival improvement in the nonGCB DLBCL subgroup.⁵² R-ACVBP was associated with more hematologic and nonhematologic toxicity. It is important to note that this regimen incorporates vindesine, an agent that is not broadly available in the USA. Until larger randomized trials confirm a benefit of treatment with R-ACVBP, R-CHOP-21 remains the standard for most patients with DLBCL.

The role of high-dose therapy (HDT) and autologous stem cell therapy (ASCT) in the frontline treatment of patients with aggressive B-cell lymphoma has also been questioned, especially within the context of modern chemoimmunotherapy. In 2008, a meta-analysis was published that included data from 15 randomized controlled trials with a total of 3079 patients treated for aggressive NHL.⁵³ Overall, treatment-related mortality was 6% in the HDT group and was not significantly different compared with conventional chemotherapy. Thirteen studies including 2018 patients showed significantly higher CR rates in groups receiving HDT, but there was no significant difference in EFS or OS in groups treated with conventional chemotherapy or high-dose chemotherapy followed by ASCT.

The question of whether patients with high-risk DLBCL may benefit from more intensive initial therapy involving HDT has also been investigated. To further define the role of HDT and ASCT, Glass et al conducted a study examining HDT plus ASCT in young (18–60 years of age) high-risk (aaIPI 2 or 3) patients with aggressive B-cell lymphoma.⁵⁴ Patients received rituximab with MegaCHOEP (cyclophosphamide, 1500 mg/m² in cycle 1, 4500 mg/m² in cycles 2–3, 6000 mg/m² in cycle 4; doxorubicin, 70 mg/m²; vincristine, 2 mg; etoposide, 600 mg/m² in cycle 1, 960 mg/m² in cycles 2–3, 1480 mg/m² in cycle 4; prednisone, 500 mg) every 21 days followed by ASCT. In this study, R-MegaCHOEP produced high 3-year OS (78.7%) and EFS (72.7%) but with considerable non-hematological toxicities.

This concept was also explored in a SWOG-led US intergroup trial investigating the benefit of autologous transplant following CHOP +/- R for advanced stage DLBCL patients with high-intermediate/high IPI score in first remission.⁵⁵ The primary study endpoints were toxicity and two-year PFS and OS for randomized patients; the study was powered to detect

a hazard ratio of 1.50 between arms. Registered patients were treated with CHOP or R-CHOP for five cycles. Patients who achieved a PR or better were randomized to one additional cycle of CHOP/R-CHOP followed by ASCT or three additional cycles of CHOP/R-CHOP. Initial results demonstrated that the addition of ASCT resulted in a significantly higher rate of PFS at 2 years (69% vs 56%) but no difference in OS (74% vs 71%).

Relapsed/Refractory

Despite our understanding of the heterogeneity of DLBCL and an increasing number of treatment combinations and experimental agents becoming available, most clinicians continue to treat DLBCL with a single management strategy at initial presentation and at relapse. Novel approaches to managing patients with relapsed DLBCL are needed.^{33,56} The question of how best to manage relapsed patients was addressed by the multicenter PARMA trial comparing ASCT to conventional salvage therapy in which 215 patients in first or second relapse were given two cycles of intensive combination chemotherapy. The 109 patients who responded were randomly assigned to receive four more cycles of chemotherapy or ASCT. With a 5-year median follow-up, EFS and OS were significantly improved with transplantation (46% vs 12% and 53% vs 32% respectively).⁵⁷ A number of standard regimens exist for salvage lymphoma therapy including ifosfamide, carboplatin, and etoposide (ICE), etoposide, methyl prednisolone, high dose cytarabine, and cisplatin (ESHAP), dexamethasone, cisplatin, and cytarabine (DHAP), and dexamethasone, cisplatin, and gemcitabine (GDP) with varying response rates.

The choice of salvage therapy is still debated although it is clear that the addition of rituximab to the re-induction regimen yields superior results. For example, the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) group randomly assigned relapsed patients to receive DHAP with or without rituximab. Following two cycles, 75% of the patients in the R-DHAP arm had responsive disease versus 54% in the DHAP arm ($P = 0.01$).⁵⁸ With a median follow-up of 24 months, there was a significant difference in PFS (52% vs 31%, $P < 0.002$) and OS in favor of the R-DHAP arm. In addition, rituximab does not appear to impair stem cell engraftment or adversely affect transplantation toxicity, and is associated with improved PFS when given prior to ASCT for DLBCL.⁵⁹ In another study validating the use of rituximab at relapse, Kewalramani et al conducted a retrospective review of patients treated with R-ICE and compared them to historical controls treated with ICE alone.⁶⁰ R-ICE given for three

cycles produced CR in 53% of patients, and no patient had R-ICE related toxicity that precluded ASCT. It is important to note that patients in both the HOVON and Kewalramani et al studies had previously received induction therapy without the addition of rituximab, whereas the studies below provide data on DLBCL patients' responses to salvage therapy when they had previously received rituximab with first-line therapy.

The choice of salvage chemotherapy after R-CHOP failures was addressed by the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL), a prospective multicenter Phase III study.⁶¹ DLBCL patients in first relapse or who were refractory after first-line therapy were randomly assigned to groups that received salvage therapy with either R-ICE or R-DHAP. After three courses of therapy, responders were treated with HDT and ASCT. The response rates for R-ICE and R-DHAP were similar, suggesting that either regimen can be used for salvage therapy. However, an analysis of the 396 patients enrolled on the trial also showed much poorer outcomes for patients who had: a second line IPI score of 2/3 vs 0/1 (3-year EFS 18% vs 40%, respectively), relapse less than 12 months after completion of first-line therapy (20% vs 45%, respectively), or prior rituximab exposure in the front line setting (21% vs 47%, respectively), regardless of the type of salvage therapy they received. Moreover, patients who relapsed early following upfront R-chemotherapy had a very poor prognosis with a 3-year PFS of 23%, and their PFS remained poor even when treatment was consolidated with HDT and ASCT (3-year PFS of 39%).⁶¹ A second randomization in this trial included 242 evaluable patients randomized to groups that were either observed or received rituximab maintenance. There was no difference in PFS (median PFS = 58.2 months with observation vs 57.6 months with rituximab, $P = 0.8314$) or OS (median OS = 62.9 months with observation vs not reached with rituximab, $P = 0.7547$) regardless of the induction regimen used. There also was no difference in PFS or OS

Table 3 Novel agents currently in clinical trials for diffuse large B-cell lymphoma

Mechanism of action	Drug(s)
Antibodies against VEGF	Bevacizumab
PKC- β inhibitor	Enzastaurin
Anti-CD22	Epratuzumab
mTOR inhibitor	Everolimus, temsirolimus
Immunomodulatory agents	Lenalidomide
Syk inhibitor	Fostamatinib
NEDD8 activating enzyme inhibitor	MLN4924
Proteasome inhibitor	Bortezomib, carfilzomib
Histone deacetylase inhibitor	Panobinostat, MGCD013

Abbreviations: mTOR, mammalian target of rapamycin; PKC- β , protein kinase C beta; VEGF, vascular endothelial growth factor; Syk, spleen tyrosine kinase.

between patients achieving a CR/CRu compared to PR. This trial indicates that rituximab maintenance does not improve EFS, PFS, or OS after ASCT following first relapse, and other data suggest that maintenance rituximab has no defined role for patients with DLBCL.⁶²

Conclusion

DLBCL remains the most commonly occurring lymphoma in the Western world. This disease is uniformly fatal without treatment, but the majority of patients are cured with standard R-CHOP chemoimmunotherapy. Debate remains regarding the role of radiation for patients with limited-stage disease, but R-CHOP-21 for six to eight cycles has clearly emerged as the standard of care for patients with advanced-stage disease. Emerging data on immunohistochemically defined subsets of DLBCL may help us to risk-stratify patients and define subtype-specific therapies in the future. While autologous stem cell transplant can salvage and cure patients with relapsed DLBCL, questions are emerging regarding the benefits of this approach for patients who relapse early after R-CHOP. Given that more patients are now cured upfront, those who relapse early may be at greater risk and more in need of novel treatment approaches.

Future directions: novel agents

At present there is no standard third-line therapy or therapy for patients with poor risk biological subtypes of DLBCL. Disease progression has been managed in such patients with a wide range of treatments including multi-agent regimens, single agents, or a variety of experimental drugs.⁶³ Recently, there has been a shift from identifying classical cytotoxic agents to molecules that target-specific pathways involved in signal transduction, apoptosis, and differentiation. The improved understanding of DLBCL subtypes and gene-expression profiles has led to the development of targeted drugs and regimens for DLBCL that may help address this clinical problem. Several novel agents are undergoing evaluation in DLBCL, both as single agents in the relapsed setting and in combination with R-CHOP. Some examples include other antibody therapies, lenalidomide, SGN-40, spleen tyrosine kinase (Syk) inhibitors, enzastaurin, histone deacetylase inhibitors, bortezomib, antisurvivin agents, bevacizumab, and mammalian target of rapamycin inhibitors (Table 3).

Lenalidomide, an approved agent that is used in myelodysplastic syndrome and myeloma, has been studied in patients with relapsed aggressive lymphomas. Phase II trials have been conducted with this agent in relapsed or refractory

aggressive NHL. In the first study, 49 patients with a median age of 65 years received lenalidomide (25 mg/day) administered on days 1–21, every 28 days for 52 weeks as tolerated, or until disease progression.⁶⁴ The most common histology was DLBCL (53%), and the overall response rate (ORR) was 35% for all patients, 19% for DLBCL patients, and 53% in mantle cell lymphoma (MCL). The estimated median duration of response was 6.2 months (range 0–12.8 months), and median PFS was 4.0 months (range 0–14.5 months). Based on the promising results of this study, an international Phase II trial was conducted with 217 patients.⁶⁵ Among 108 patients with DLBCL, 28% responded and 7% achieved a CR. The PFS was 2.3 months. The drug was tolerated well and the toxicity profile was similar to the earlier trial. The clinical data available so far suggest that lenalidomide is a promising drug for lymphoma therapy. Lenalidomide is also being investigated in combination with R-CHOP⁶⁶ and as a maintenance therapy for patients with DLBCL.

Bortezomib, a proteasome inhibitor that demonstrated single-agent activity leading to its approval for use in relapsed MCL,⁶⁷ is another agent hypothesized to have activity in DLBCL based on molecular profiling. ABC and primary mediastinal DLBCL subtypes are known to have high levels of activity in the NF- κ B pathway, which is targeted by bortezomib. Furman et al completed a Phase I/II study of bortezomib-R-CHOP in patients with previously untreated DLBCL or MCL.⁶⁸ Based on Phase I results, bortezomib at 1.3 mg/m² combined on days one and four with the standard R-CHOP regimen given in a 21-day cycle was recommended for further study, and 76 additional patients, including 40 patients with DLBCL, were enrolled in the phase 2 portion of the study. Of 35 response-evaluable DLBCL patients, the ORR was 100%, and 90% of patients had a CR (17 patients) or an unconfirmed CR (eleven patients). Thirty-one of these evaluable patients had a tumor subtyped as GCB or non-GCB using the Hans method. In the 17 patients with the non-GCB subtype the 2-year PFS (approximately 70%) and 2-year OS (approximately 85%) were similar to those of the 14 patients with the GCB subtype, suggesting that the addition of bortezomib to R-CHOP improved the outcome of this group that had a poor prognosis.

A European-based Phase II study randomized 49 newly diagnosed B-cell lymphoma patients to four bortezomib schedules in combination with R-CHOP.⁶⁹ Across these schedules an 88% CR/CRu rate was reported for 16 patients with aggressive lymphoma (DLBCL and transformed follicular lymphoma). Dunleavy et al conducted a Phase I/II study of bortezomib with dose-adjusted administration of etoposide, vincristine, and doxorubicin for 96 hours with

bolus doses of cyclophosphamide and oral prednisone in patients with relapsed aggressive lymphoma.⁷⁰ This study enrolled 33 DLBCL patients and the ORR was approximately 40%. However, 27 patients had GCB/non-GCB subtyping performed and this indicated that the typically poor outcome, non-GCB subtype was particularly sensitive to this combination. The ORR favored non-GCB over GCB (83% vs 13%, $P = 0.0004$), as did the CR rate (42% vs 7%). There was also a significant difference in OS favoring the non-GCB subtype ($P = 0.0026$). The results of this study are the opposite of what may have been expected, with the poor prognosis (non-GCB) group achieving superior outcomes.

In the Phase I/II trial described above, patients with non-GCB DLBCL had similar PFS and OS to GCB patients when bortezomib was added to RCHOP,⁷¹ suggesting that bortezomib may help to overcome the adverse outcomes associated with the ABC subtype. A multicenter clinical trial using the Hans method to subtype DLBCL patients and randomize non-GCB patients to groups to be treated with either bortezomib plus R-CHOP or R-CHOP is underway at the time of this publication.

Enzastaurin (LY317615.HCl), an acyclic bisindolyl maleimide, is a potent small-molecule inhibitor of serine/threonine kinases that functions by competing with adenosine-5'-triphosphate for the enzyme's adenosine-5'-triphosphate-binding site. It was initially developed as a selective inhibitor of protein kinase C β , with a 50% inhibitory concentration of 6 nmol/l, and it also inhibits other protein kinase C isoforms at higher concentrations. Robertson et al reported the first multicenter Phase II study of enzastaurin in patients with relapsed or refractory DLBCL.⁷² Enzastaurin was given orally once daily until disease progression or unacceptable toxicity occurred. Study endpoints included freedom from progression for two or more 28-day cycles, objective response, and toxicity. Treatment with enzastaurin was well tolerated, and a small subset of patients benefited from the treatment. Phase III studies are now being conducted that include testing of daily enzastaurin versus placebo for the prevention of relapse in DLBCL, combination trials of enzastaurin with rituximab, and a trial of combination with rituximab, gemcitabine and oxaliplatin (R-GEMOX).

B-cell receptor-mediated survival signals are another target that has been identified through gene-expression profiling, and this can be blocked by fostamatinib disodium, an inhibitor of Syk that induces apoptosis in B-cell lymphoma cell lines and primary tumors. Fostamatinib disodium, the first clinically available oral Syk inhibitor, was recently tested

in patients with recurrent B-cell NHL. Dose-limiting toxicity in the Phase I portion was associated with neutropenia, diarrhea, and thrombocytopenia, and 200 mg bid was chosen for Phase II testing. Sixty-eight patients with recurrent B-NHL were then enrolled in three cohorts: DLBCL; FL, and "other" NHL (mantle MCL; marginal zone/MALT; lymphoplasmacytic; and SLL/CLL). Common effects of toxicity included diarrhea, fatigue, cytopenias, hypertension, and nausea. Objective response rates were 22% for DLBCL, 10% for FL, 55% for SLL/CLL, and 11% for MCL. The median PFS was 4.2 months, and the median response duration exceeded 4 months.⁷³

Although no particular chemical entity has emerged as a standard therapy for patients with DLBCL who fail ASCT or are ineligible for transplant, a number of compounds including those discussed above hold promise for the management of DLBCL in the future. Numerous trials are needed to determine the best ways to sequence these therapies, evaluate their efficacy as single agents, determine the best use of these compounds in combination with standard chemotherapy regimens, or develop novel combination regimens. While the majority of patients are now cured of DLBCL with R-CHOP upfront, and a substantial fraction of patients are cured with ASCT at relapse, a number of new agents promise are needed to improve outcomes for poor risk patients with DLBCL.

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