

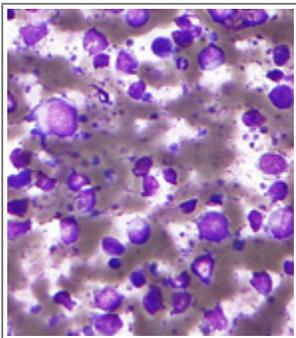
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REVIEW ARTICLE

Diffuse Large B-Cell Lymphoma: Current Treatment Approaches

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ABSTRACT: Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring lymphoid malignancy. While a series of trials support R-CHOP (cyclophosphamide, [doxorubicin \(Drug information on doxorubicin\)](#), vincristine, and [prednisone \(Drug information on prednisone\)](#), plus [rituximab \(Drug information on rituximab\)](#))-21 as the standard of care for all patients, DLBCL has substantial biological and clinical heterogeneity, leading to marked differences in outcomes for disease subgroups. We examine clinical, biological, and functional imaging techniques for risk-stratifying patients, and we review approaches for dose intensification in the rituximab era that are aimed at improving outcomes for poor-risk patients. Together, the results achieved with these measures indicate no particular benefit for administering R-CHOP-14 vs R-CHOP-21 in older or younger patients with DLBCL, highlight opportunities for future studies of young patients with high-risk DLBCL, and suggest the promise of biologic risk stratification. Such approaches will provide key opportunities for further advances in the treatment of DLBCL, given that chemotherapy intensification appears to provide limited additional benefits over the current standard of care.

Introduction



Micrograph of a diffuse large B-cell lymphoma, lymph node FNA specimen, field stain; source: Nephron, Wikimedia Commons

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring lymphoid malignancy and accounts for one-third of adult cases of non-Hodgkin lymphoma (NHL). It is regarded as an aggressive lymphoma, characterized by rapid growth and limited survival in the absence of treatment or with

inadequate treatment.[1] DLBCL is both biologically and clinically heterogeneous, with at least three important subtypes (activated B-cell [ABC], germinal center B-cell [GCB], and primary mediastinal large B-cell lymphoma [PMBL]), features of which carry predictive and prognostic relevance. A substantial number of patients are cured with standard anthracycline-based chemotherapy, and with the addition of rituximab (R; Rituxan) to [cyclophosphamide](#)([Drug information on cyclophosphamide](#)), doxorubicin, vincristine, and prednisone (CHOP), there have been significant improvements in clinical outcomes, including overall survival (OS).[1-4] However, a significant portion of high-risk patients still fail to achieve the desired response to induction therapy and have a poor prognosis with current standard treatments. We examine clinical and biological features of DLBCL patients with poor outcomes, and we review recent studies addressing alternatives to standard front-line management strategies together with unresolved questions.

Defining Poor-Risk Subgroups of DLBCL

Clinical prognostic factors

Developed in the 1990s, the international prognostic index (IPI) is the most functional clinical tool used to predict outcome for patients with DLBCL.[5] This model was derived from a pooled analysis of more than 2000 patients with aggressive lymphoma (mainly DLBCL) treated with an anthracycline-containing chemotherapy regimen between 1982 and 1987. Clinical features that were predictive of OS and relapse-free survival were identified and include: age, stage, serum lactate dehydrogenase (LDH), performance status, and number of extranodal disease sites. Patients are scored based on these clinical features and can then be stratified into one of four discrete groups with 5-year predicted survival rates of 73%, 51%, 43%, and 26%.[5] In addition, this index has enabled comparisons of published study results, and it supports trials designed to classify patients with similar characteristics and expected outcomes. A question that has been raised is whether the IPI remains prognostic in the rituximab era. Sehn et al performed a retrospective analysis of patients with DLBCL treated with R-CHOP and redefined three outcome categories, termed the revised IPI, which was a more clinically useful predictor of outcome than the IPI in this population.[6] All groups had a predicted 4-year OS greater than 50%. A more recent analysis of more than 1000 patients treated with chemo-immunotherapy suggests that the IPI is useful in the rituximab era for predicting event-free survival (EFS), progression-free survival (PFS), and OS.[7] The IPI continues to be an important tool for clinicians to use to risk-stratify patients and to provide the prognostic information that is often requested by patients in consultation. At present, this index remains central to the design and interpretation of DLBCL clinical trials, by facilitating identification and classification of discrete patient populations.

Other clinical factors also may have prognostic significance. In addition to its use in the IPI, age has been one of the most robust adverse prognostic features in NHL. Numerous studies have associated older age with inferior outcomes, including OS.[8-11] One may speculate that reasons for worse survival among older individuals with DLBCL include the higher incidence of comorbid conditions, poorer performance status, and possibly inferior treatment prescribed, given concerns about the ability of older individuals to tolerate aggressive regimens. A retrospective analysis of very elderly patients (> 80 years; median, 83 years) reported that this patient population presented with similar clinical and prognostic features as younger patients, but they had significant differences in disease management compared with their younger counterparts.[12] The authors concluded that the majority of deaths were attributed to progressive disease and that age was the limiting factor in prescribing effective treatment. With the expanding life expectancy and aging population, the significance of age and its implications for outcomes will only increase in importance, and clinical trials are needed to address this question.

Race also may influence the prognosis of DLBCL. Notably, African-American patients with DLBCL in the US present at a younger age and more advanced stage, and they have inferior survival.[13,14]

Among 37,009 DLBCL cases diagnosed from 1992 to 2005 in the Surveillance, Epidemiology, and End Results (SEER) registry, the majority of African-American patients presented with stage III/IV disease (54%), and 5-year survival rates were 38% for black vs 46% for white patients ($P = .02$).^[14] Disparities in outcomes have been observed even when the same treatment is administered to black vs white patients.^[15] What has not been clearly elucidated to date is whether racial and age variances are a result of differences in tumor biology that can explain inferior outcomes or are a reflection of disparities in socioeconomic status or other nonclinical factors that influence outcome. Future studies are needed to examine interactions between these and other clinical factors and biological predictors of differences in presentation and outcome for patients with DLBCL.

Biological factors and functional imaging

Despite their practical value in distinguishing DLBCL patients, prognostic clinical features are likely surrogate markers for biological heterogeneity or composite measures that mix the influences of tumor biology, clinical factors, and nonclinical factors. Over the past decade there have been significant efforts to define biologically relevant subgroups of DLBCL that can lead to rational therapeutic strategies. Distinct gene-expression patterns have been defined using hierarchical clustering from DNA microarrays that reflect differences in cell of origin, proliferation rate, and host immune response to the tumor, and which can be used as molecular predictors of survival.^[16] The encompassing diagnosis of DLBCL can now be subdivided by gene-expression profiling (GEP) into at least three molecular subtypes: ABC, GCB, and PMBL DLBCL. When treated with CHOP-like regimens, patients in the GCB subgroup had better 5-year survival rates than patients with ABC DLBCL (OS, 60% vs 35%, $P < .001$), independent of IPI risk.^[16] Additional studies using GEP as predictors of survival have confirmed these findings and expanded upon them.^[17-19] An analysis from the Lymphoma/Leukemia Molecular Profiling Project performed GEP on 233 tumor biopsy samples from patients with DLBCL treated with R-CHOP.^[20] A multivariate gene-expression-based survival model predicted a favorable prognosis for a GCB signature and paralleled the distinction between ABC and GCB in studies prior to the ubiquitous use of rituximab.^[20] In addition, differences in immune cells, fibrosis, and angiogenesis in the tumor microenvironment also may influence survival in DLBCL.

With improved technology that allows for GEP of [paraffin \(Drug information on paraffin\)](#)-embedded tissue, more comprehensive analysis may be possible in the future, with further exploration of clinically significant biomarkers.^[18] However, routine clinical application of GEP is not currently widespread; instead, extrapolation of gene-expression results to immunohistochemistry (IHC) algorithms is more practical and appears to determine the cell of origin in the majority of cases.^[21-23] Individual biomarkers, including BCL2, BCL6, p21, and c-myc, also have prognostic significance in DLBCL.^[24-27] Present in 10% to 20% of cases, c-myc expression or amplification portends a poor prognosis, with OS less than 30% at 2 years. When it is associated with additional unfavorable biomarkers, such as BCL2, it results in an extremely poor prognosis. Discerning cell-of-origin phenotypes is particularly important for identifying poor-risk patients, so that rational therapeutic strategies can be developed and employed.

Functional imaging may be another approach for risk-stratifying patients at diagnosis or early in the course of therapy. While positron emission tomography (PET) with [¹⁸F] fluorodeoxyglucose (FDG) is often part of staging and assessment of DLBCL, there has been interest in using interim PET assessment to identify patients who are at high risk for refractory disease or relapse after standard therapy. National Comprehensive Cancer Network (NCCN) guidelines currently include the use of interim PET/CT after 2 to 4 cycles of therapy.^[28] Evidence for the use of PET assessment during chemotherapy has been limited by study heterogeneity and conflicting results.^[29] Further exploration of this question has raised additional questions regarding the value of interim PET scans for defining prognosis and supporting decision making. Ghesquière et al investigated whether the use of interim or post-treatment completion

PET had an association with prognosis.[30] Consistent with previous findings, a positive PET following completion of initial therapy was associated with a poorer prognosis compared with patients with a negative PET (5-year OS, 50% vs 84%, $P = .001$). These findings are in contrast to a prospective trial from Memorial Sloan-Kettering in which patients with residual FDG-PET–positive disease after 4 cycles of accelerated R-CHOP underwent a repeat biopsy.[31] The results of the interim FDG-PET assessment did not correlate with PFS, and only 5 of 38 patients with positive scans had positive biopsies; the remaining tissue specimens showed inflammation. A phase II trial conducted by Stewart et al ($n = 67$) tested the use of PET/CT to guide the use of high-dose sequential induction therapy with autologous stem cell transplant (ASCT).[32] Patients with an unfavorable interim PET/CT after two cycles of R-CHOP received R-DICEP (rituximab, dose-intensive cyclophosphamide, etoposide, cisplatin) followed by R-BEAM (rituximab, [carmustine\(Drug information on carmustine\)](#) [BCNU], [etoposide\(Drug information on etoposide\)](#), Ara-C [cytarabine], [melphalan\(Drug information on melphalan\)](#))/ASCT while those with a favorable interim PET/CT received an additional 4 cycles of R-CHOP. With a median follow-up of 24 months, there was no significant difference in 2-year PFS between patients with unfavorable or favorable interim PET/CT, suggesting that PET-directed aggressive therapy for poor-risk patients may overcome the expected poor outcomes for this group. However, these findings remain premature and conflict with the results of the Memorial Sloan-Kettering study. Another limitation of interim PET assessment is reproducibility. The results of a blinded, independent review of the Eastern Cooperative Oncology Group (ECOG) study E3404 revealed that one-third of the time, the expert panel of nuclear medicine physicians disagreed on the interpretation of the interim scans despite using consensus criteria.[33] In the absence of clear evidence that supports the routine practice of interim PET outside of a clinical trial, caution is advised regarding the use of this information to define prognosis or as a basis for treatment decisions.

Dose-Dense and Dose-Intense Treatment Strategies

Although poor-risk DLBCL can be defined in a number of ways (as noted above), there clearly exists a population of patients who experience unfavorable outcomes with standard therapy. In an attempt to improve on the results seen, investigators have explored dose-dense and dose-intense strategies and consolidation with high-dose therapy (HDT) followed by rescue with ASCT to reduce relapse rates. Some early phase II studies in the US and randomized phase III studies in Europe suggested that better outcomes could be achieved with this approach compared with standard CHOP repeated every 21 days (CHOP-21).[34-38] However, nearly two decades ago, the US Intergroup study demonstrated that CHOP was associated with an OS similar to that of more intensive (and more complicated) regimens and was better tolerated, thus establishing CHOP as the standard of care. Nevertheless, outcomes remained disappointing for some patients, with 30% of patients being refractory or progressing shortly after induction, and patients experiencing 30% to 40% OS at 5 years.[39]

In selected settings, the addition of etoposide to CHOP,[40] shortening the administration of CHOP to a biweekly interval (CHOP-14),[37] and use of a more intensified anthracycline regimen,[36,41] did demonstrate advantages over standard CHOP, but these approaches were not broadly adopted.

A major development in the treatment of DLBCL occurred when rituximab was assessed in phase II studies of aggressive B-cell lymphomas.[42,43] Several groups launched phase III studies in different DLBCL patient subsets to investigate the impact of rituximab.[2,4,44] One of the earliest reports of survival benefit was from the Groupe d'Étude des Lymphomas de l'Adulte (GELA), showing that DLBCL patients over 60 years of age who were treated with R-CHOP had superior outcomes compared with patients treated with CHOP.[4] With more mature results, OS, EFS, and PFS remained superior with the addition of rituximab, and no significant increase in adverse events was reported.[45] Given the

improvement in outcomes with dose-dense and dose-intense strategies prior to the use of rituximab in this setting, studies followed that investigated whether the addition of rituximab could extend the benefits described.

One such trial, published by Economopoulos et al, began enrollment in 1999 and randomized patients to CEOP (cyclophosphamide, [epirubicin](#) (Drug information on epirubicin), vincristine, and prednisone) every 2 weeks (CEOP-14) vs a standard 3-week cycle (CEOP-21).[46] All patients enrolled from May 2002 onward received rituximab with each chemotherapy cycle, and patients achieving a complete response (CR) received rituximab consolidation. Response rates (CR rate, 51% CEOP-14 vs 53% CEOP-21, $P = .786$) and survival were similar between the two arms, demonstrating no difference with the dose-dense/intense approach. While the addition of rituximab to both the 14-day and the 21-day regimens improved time to progression and OS, no difference emerged between the arms. A dose-dense strategy also was explored in the RICOVER-60 trial.[3] Based on prior success with CHOP-14, the German High Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) randomized elderly patients (61 to 80 years) to receive 6 or 8 cycles of CHOP-14, with or without rituximab. Six cycles of R-CHOP-14 significantly improved 3-year EFS (66.5% vs 47.2%), PFS (73.4% vs 56.9%), and OS (78.1% vs 67.7%) compared to 6 cycles of CHOP-14, and there was no benefit from extending therapy to 8 cycles of R-CHOP-14 (compared to 6 cycles of R-CHOP-14). A significant challenge in interpreting the results of this study was the lack of comparison with R-CHOP-21, a standard approach in the US and many other countries.

Dr. David Cunningham, on behalf of the United Kingdom National Cancer Research Institute Lymphoma Clinical Study Group, presented results from a randomized phase III study comparing R-CHOP-14 to the standard R-CHOP-21 at the American Society of Clinical Oncology (ASCO) 2011 conference.[47] Between March 2005 and November 2008, a total of 1080 treatment-naïve patients were randomized to either 8 cycles of standard R-CHOP-21 or 6 cycles of R-CHOP-14 plus granulocyte colony-stimulating factor (G-CSF), with an additional 2 cycles of single-agent rituximab (as was given in RICOVER-60). This study was designed to detect an 8% improvement in 2-year OS for the superior regimen. The trial arms were balanced with respect to patient age, presence of B symptoms, bulky disease, stage, and IPI, and 52% of patients were 60 years of age or older. Overall response rates (ORRs) were similar between the two arms: CR or CRu (complete response, unconfirmed) was 63% with R-CHOP-21 vs 58% with R-CHOP-14 ($P = .15$). After a median follow-up of 37 months, PFS ($P = .98$) and OS ($P = .78$) were similar, and subgroup analyses failed to identify a subset of patients who benefited from the accelerated R-CHOP regimen. Grade 3/4 nonhematologic toxicities were comparable in the two arms. Among patients receiving the 21-day regimen, however, there was a significantly greater frequency of grade 3/4 neutropenia (77% vs 37%) and febrile neutropenia (11% vs 5%), respectively ($P < .01$ for both), compared with the 14-day regimen. The lower frequency of neutropenia in the R-CHOP-14 arm is likely a reflection of prophylaxis with G-CSF administered to all patients in this group. In addition, there were higher incidences of thrombocytopenia (5% vs 9%) and anemia (1% vs 3%) in the R-CHOP-14 arm, likely a consequence of treatment intensity. The authors concluded that based on these data, there is no evidence to support a shift from the standard R-CHOP-21 to an accelerated R-CHOP strategy.

Similar findings were presented in 2009 at the annual American Society of Hematology (ASH) convention by the GELA, which described the results of the planned interim analysis of the LNH03-6B, an open-label, randomized trial evaluating the efficacy of R-CHOP-14 compared to R-CHOP-21 in elderly patients (median age, 72; range, 60–80 years).[48] Patients were randomized to 8 cycles of R-CHOP-14 or R-CHOP-21, with a second randomization to prophylactic darbepoietin alfa vs conventional treatment for chemotherapy-induced anemia. A secondary endpoint of the study was to examine whether maintaining a hemoglobin level of 13 g/dL renders patients better able to tolerate the dose-dense regimen.

At baseline, more patients in the R-CHOP-14 arm had an age-adjusted IPI (aaIPI) score of 2 to 3 (67% vs 59%), and more patients in the R-CHOP-21 arm presented with B symptoms (43% vs 37%); otherwise, patient characteristics were similar in the two groups. At 2 years, there was no significant difference in ORR (81% with R-CHOP-14 vs 84% with R-CHOP-21), PFS (49% vs 63%), or OS (67% vs 70%). Grade 3/4 hematological toxicity was more frequent in the R-CHOP-14 group, similar to the United Kingdom trial. Unlike the United Kingdom trial, white blood cell growth factor support was not routinely required for patients who received R-CHOP-14, raising some questions about R-CHOP-14 administration in this trial. Taken together, these results indicate no particular benefit to administering R-CHOP-14 rather than R-CHOP-21 for older or younger patients with DLBCL.

An alternative dose-intensive strategy for treatment-naïve patients with DLBCL is based on trials conducted prior to the rituximab era that demonstrated superiority of the intensive regimen ACVBP (doxorubicin [Adriamycin], cyclophosphamide, [vindesine \(Drug information on vindesine\)](#), [bleomycin \(Drug information on bleomycin\)](#), and prednisone) over standard CHOP.[36,41] In 2003, the GELA initiated a multicenter, phase III, open-label, randomized trial comparing the efficacy and safety of R-ACVBP vs R-CHOP in younger patients with an aaIPI of 1. Compared to R-CHOP-21, the R-ACVBP regimen produced superior 3-year EFS (81% vs 67%, $P = .0035$) and OS (92% vs 84%, $P = .0071$). However, R-ACVBP was associated with substantially more hematologic and nonhematologic toxicity, and this regimen incorporates vindesine, an agent that is not widely available in the US and therefore has not been broadly adopted. Another intensive regimen developed by investigators at the National Cancer Institute (NCI) focused on pharmacokinetics to overcome drug resistance in DLBCL, using dose-adjusted (DA) etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (EPOCH), and rituximab (DA-EPOCH-R). The doxorubicin, etoposide, and vincristine in this regimen are infused over a period of 96 hours and are pharmacodynamically dose-adjusted based on the neutrophil level nadir. In a phase II trial of 72 previously untreated patients with DLBCL, this approach demonstrated high 5-year PFS and OS.[49] The Cancer and Leukemia Group B (CALGB) reproduced the NCI results in a multi-institutional phase II study; 5-year OS rates were 84%, and the regimen was tolerated without significant grade 4 nonhematologic toxicities.[50] An ongoing phase III trial (CALGB 50303) comparing R-CHOP vs DA-EPOCH-R in patients with newly diagnosed DLBCL (examining outcomes in ABC and GCB subtypes) will provide a systematic comparison of these two regimens.

Another approach to intensifying the initial treatment for DLBCL involves consolidation following induction with HDT and ASCT. The role of ASCT in frontline therapy for DLBCL has been unclear, particularly in the era of immunochemotherapy. While consolidation with HDT and ASCT has been shown to reduce relapse rate in DLBCL in some settings,[38,51] first-line ASCT has been challenged by a meta-analysis published in 2008, in which a total of 3079 patients from 15 randomized trials were included.[52] Despite better rates of CR, the EFS and OS were the same regardless of whether patients were treated with conventional chemotherapy or HDT followed by ASCT.

Additional data from the results of the SWOG-led Intergroup phase III trial S9704 were presented at the 2011 ASCO conference. This trial investigated the benefits of autologous transplant in first remission in patients with advanced-stage diffuse aggressive NHL with high-intermediate/high IPI score, following 5 cycles of CHOP with or without rituximab (CHOP±R).[53] Between September 1997 and December 2007, a total of 370 patients were enrolled (median age, 51 years); 59% were male, 62% had stage IV disease, 85% had an elevated LDH level, and 32% had a high IPI score after adjusting for age. Of those eligible, 253 patients were randomized following standard therapy to CHOP±R × 3 additional cycles ($n = 128$) or transplant ($n = 125$) involving CHOP±R × 1 followed by ASCT using TBI- or BCNU-based conditioning regimens. Initial results demonstrated that the addition of ASCT resulted in a significantly higher PFS at 2 years (69% vs 56% [hazard ratio (HR) 1.72, 1.18–2.51]; $P = .005$), but no difference in 2-year OS was seen (74% vs 71%, [HR 1.24, 0.81–1.91]; $P = .32$). Possible confounders to the OS data included 18% of patients in the standard arm who underwent salvage therapy with ASCT at relapse and

TABLE 2

Management Recommendations for Patients With Advanced DLBCL

Since modifying traditional approaches has not provided the hoped-for therapeutic benefit, what can be said about novel approaches? First, can we be more effective at risk stratification? Risk stratification based on clinical features, such as IPI, is useful particularly in standardizing patients enrolled in clinical trials, but it may be less promising than biologic risk stratification when making treatment decisions. To ensure that patients are informed, treatment decision-making should include discussions about the significance of the cell of origin and projected outcomes with standard induction therapy, based on molecular subtype. Given the rather dismal outlook for DLBCL patients with the ABC subtype, enrollment in a clinical trial should be strongly encouraged. Applying the knowledge we have gained from GEP, therapeutic targeting of molecular pathways may ultimately lead to improvement in outcomes in DLBCL. Several novel agents exploiting this strategy are undergoing evaluation, both as single agents in the relapsed-disease setting and in combination with R-CHOP.[57] Some examples include immunomodulatory drugs (IMiDs), spleen tyrosine kinase (Syk) inhibitors, Bruton's tyrosine kinase inhibitors, protein kinase C inhibitors, histone deacetylase inhibitors, proteasome inhibitors, anti-survivin agents, mTOR (mammalian target of rapamycin) inhibitors, and alternative antibody therapies. With the expanding information on the pathophysiology of and biomarkers for DLBCL, future studies should build upon these biologic underpinnings with rational study design and novel therapeutics. Such approaches will provide key opportunities for further advances in the treatment of DLBCL, given that chemotherapy intensification appears to provide limited additional benefits over the current standard of care.

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