State-of-the-Art Therapeutics: Diffuse Large B-Cell Lymphoma

Bertrand Coiffier

ABSTRACT

This article is a review of the improvement in the treatment of patients with diffuse large B-cell lymphoma made during the last 10 years. Patients with diffuse large B-cell lymphoma now have a better outcome with longer survival because of two major developments: (1) increasing the dose of active drugs with shortening the time between cycles, resulting in dose-dense and/or dose-intense regimens; and (2) combining rituximab with chemotherapy. Both strategies were associated with higher response rates, lower relapse rates, longer event-free survival, longer time to progression, and longer overall survival, particularly in patients without adverse prognostic parameters. A combination of dose-dense, dose-intense regimens plus rituximab is currently being tested for poor-risk patients with diffuse large B-cell lymphoma. However, much work has to be done for patients with high-risk lymphoma. It may come with a better definition of genetic abnormalities specifically associated with refractoriness to chemotherapy.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most frequent non-Hodgkin’s lymphoma subtype, accounting for 30% to 35% of all cases. It is characterized as an aggressive lymphoma because survival is limited in the absence of effective treatment. Currently, DLBCL may be cured in a significant percentage of patients, depending on the initial characteristics of the tumor and the host. The treatment of DLBCL has been revolutionized in recent years with the addition of rituximab to combination chemotherapy, resulting in an increased proportion of cured patients. Despite these advances, therapeutic challenges persist, particularly for patients with the highest risk of failure. In this review, new developments will be presented together with questions to be resolved.

PROGNOSTIC FACTORS AND CHOICE OF TREATMENT

The description of the International Prognostic Index (IPI) for diffuse aggressive lymphoma in 1993 enabled comparisons of published results and the prospective design of studies including patients with like characteristics. Age, one of the five parameters in the index, is also an important determinant in the choice of treatment because older patients may have comorbid conditions. On this basis, the age-adjusted IPI (aa-IPI), which is based on stage, serum lactate dehydrogenase level, and performance status, was also validated by the international consortium. Patients with an aa-IPI score of 0 have favorable, localized disease; those with an aa-IPI score of 1 constitute a group with intermediate prognosis; and those with an aa-IPI at 2 or 3 have the worst prognosis. Of note, immunophenotype was not considered in the design of the IPI, but T-cell lymphomas, which have been associated with a worse outcome in all prospective and retrospective analyses, comprise only a small subset of diffuse aggressive lymphoma. Before the incorporation of rituximab in DLBCL, patients with aggressive B-cell...
or T-cell lymphoma were treated similarly with doxorubicin-containing combination chemotherapy. Whether a particular presentation or site (mediastinal, gastrointestinal, nodal, or extranodal) would benefit from a specific regimen or strategy was never adequately studied or proven, with the possible exception of primary CNS lymphoma. This was also the case for the different histologic entities within the DLBCL or peripheral T-cell lymphomas.

Although gene expression analyses have defined subtypes of DLBCL on the basis of cell of origin, with different outcomes after treatment with combination chemotherapy, this technology is not widely available or, at this time, practical for routine clinical use. However, molecular profiling allows recognition of important gene signatures involved in the pathobiology of DLBCL and the identification of potential new therapeutic targets. Extrapolation of gene expression results to an immunohistochemistry platform has more immediate potential for clinical application.5

Development of Dose-Dense and Dose-Intense Regimens

In 1993, the US Intergroup study4 demonstrated that the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) was associated with similar complete response (CR) rates, progression-free survival (PFS), and overall survival (OS) compared with more complicated regimens associated with more toxicity. However, CHOP resulted in only a 30% to 40% overall survival at 5 years, and 30% of patients failed to respond or progressed shortly after the completion of treatment. These outcomes prompted the investigation of dose-dense or dose-intensive strategies to improve response rates or consolidation with high-dose therapy (HDT) with autologous transplantation to decrease the relapse rates. Even though these therapeutic regimens have not been applied broadly, particularly in the United States, they have demonstrated significantly better results in many cases.5 Several phase II studies in the United States and randomized phase III studies in Europe have demonstrated superiority of these approaches over the CHOP regimen, as described in more detail in the following paragraphs.6-10

The Rituximab Effect

After the demonstration of the activity of rituximab in aggressive B-cell lymphomas in two phase II studies,11,12 one with rituximab alone in relapsing patients and the other with rituximab (R) -CHOP in untreated patients, several groups launched randomized trials in different patient subsets to test the ability of R-CHOP to increase the cure rate over CHOP alone in DLBCL. The first report of a significant benefit for patients treated with R-CHOP was a preliminary analysis from the Groupe d’Etude des Lymphomes de l’Adulte (GELA) in 2000 in elderly DLBCL patients.13 Since then, the results from two large phase III studies and one population-based study have confirmed the superior efficacy of the combination of rituximab and CHOP in DLBCL patients, setting this as the new standard of care.14-18

The results from GELA are currently the more mature, with a 5-year median follow-up.19 Nearly half of R-CHOP patients are event free at 5 years, compared with 28% in the CHOP arm (Table 1). Event-free survival (EFS), PFS, disease-free survival (DFS), and OS remained statistically significant in favor of the combination of R-CHOP with P values of .00002, < .00001, .00031, and .0073, respectively (Fig 1). The benefit from R-CHOP was observed in both low-risk and high-risk aa-IP screening (Fig 2). No additional long-term toxicity appeared to be associated with the R-CHOP combination.

Good-Risk Patients

Patients with an aa-IP score of 0 or 1 have either localized disease or disseminated disease with favorable features (normal lactate dehydrogenase [LDH] level and good performance status). For patients with nonbulky stage I-II diffuse aggressive lymphoma, three cycles of CHOP followed by involved-field radiation therapy became a standard after the study conducted by the Southwest Oncology Group (SWOG).20 The Eastern Cooperative Oncology Group (ECOG) study evaluated eight cycles of CHOP with or without consolidative radiation therapy in complete responders who presented with unfavorable stage I (bulky or mediastinal or retroperitoneal) or stages IE, II, or IIE disease. In this study, which was underpowered, DFS was greater for radiation-therapy patients at 6 years (73% vs 56%, two-sided P = .05), but differences in OS were not significant.21

GELA compared three cycles of CHOP plus involved-field radiotherapy with the ACVBP (doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone)
A chemotherapy regimen with sequential consolidation in 747 previously untreated patients < 61 years of age with stage I to II aggressive lymphoma and an aa-IPI of 0.22. With a median follow-up of 7.7 years, EFS and OS were significantly longer in the chemotherapy-alone group ($P < .001$ and $P = .001$, respectively). The 5-year estimates of EFS were 82% for patients receiving chemotherapy alone and 74% for patients treated with CHOP plus radiotherapy. The 5-year estimates of OS were 90% and 81%, respectively (Fig 3). In a multivariate analysis, EFS and OS were affected by treatment arm independent of stage and tumor bulk. In this study, ACVBP followed by sequential consolidation was superior to three cycles of CHOP plus radiotherapy in low-risk localized lymphoma in patients younger than 61 years.

GELA has conducted another study in elderly patients that also tests the benefit of the radiotherapy. In the LNH-93.4 study, patients > 60 years of age were randomly assigned to either four cycles of CHOP or four cycles of CHOP plus involved-field radiotherapy. Patients had stage I or II disease and an aa-IPI of 0. In a preliminary analysis, CR rates, EFS and OS were similar in both groups.23 These randomized prospective studies have studied different populations of localized diffuse aggressive lymphoma, leading to variable interpretation. In patients with favorable, nonbulky stage I disease, either limited chemotherapy and radiation therapy or a longer course of chemotherapy alone are likely to yield similar long-term results. In localized disease patients with bulky tumor or IPI risk factors, a full course of chemotherapy is indicated and, to date, radiation therapy consolidation has not demonstrated a survival advantage in these patients. The most important question currently relates to the added benefit of rituximab in these patients. It is GELA’s practice to use six cycles of R-CHOP for elderly patients who cannot tolerate a more aggressive chemotherapy regimen. In younger patients, the current LNH-03.2B study is comparing six to eight cycles of R-CHOP with a more intensive rituximab chemotherapy regimen in good-risk aa-IPI.

Two additional studies are pertinent to the discussion of good risk patients. The German Non-Hodgkin’s Lymphoma Study Group evaluated CHOP administered on a 2- or 3-week schedule and the addition of etoposide (CHOEP), also on a 2- or 3-week schedule, in younger patients (age 18 to 60 years) with diffuse aggressive lymphoma and a normal LDH.24 About two thirds of the study group had an aa-IPI of 0. In this study, which also included other histologic subtypes and some T-cell lymphomas, the addition of etoposide resulted in superior response rates and EFS, but similar OS at 5 years. As noted in the following paragraphs, CHOEP and CHOP have been evaluated in combination with rituximab in the MabThera International Trial (MiNT), whereupon the differences in these regimens were no longer apparent.25
Fig 2. (A) Event-free survival, (B) progression-free survival, and (C) overall survival with a median follow-up of 5 years in patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and CHOP in the LNH-98.5 study according to the age-adjusted International Prognostic Index score at diagnosis: graphs on left, low-risk patients (scores 0 and 1); graphs on right, high-risk patients (scores 2 and 3). All differences are statistically significant except for overall survival in high-risk patients: $P$ values are .00085, .0037, .00013, .00078, .023, and .062, respectively, from left to right. Adapted with permission, Feugier et al.19
Elderly Patients With Poor-Risk DLBCL

Classically, elderly patients are defined by age older than 60 years. They represent 50% of patients with aggressive lymphoma. A subgroup of patients older than 80 years has currently been defined because these patients will be seen more frequently in the future and the strategy in these elderly patients may be different from the standard therapy in patients in the age group of 61 to 79 years.

Currently, two studies have demonstrated that the combination of rituximab with CHOP is clearly superior to CHOP alone.13,14,19 The first study, reported by GELA, was described in the Rituximab Effect section and in Table 1 and Figures 1 and 2. The second study, the US Intergroup E4494 study from ECOG and Cancer and Leukemia Group B (CALGB) with participation from SWOG, has been reported in abstract form.14 The E4494 study compared CHOP with R-CHOP; and, for responding patients, maintenance with rituximab alone, four infusions every 6 months for 2 years versus observation. E4494 differs in several ways from the GELA study: (1) rituximab was administered according to the original R-CHOP study by Czuczman et al,26 resulting in four to five rather than eight rituximab infusions; (2) patients in CR at four cycles received a total of six cycles of CHOP; and (3) half of responding patients received maintenance with rituximab. Patients had nearly the same characteristics as the GELA study; the distribution of high-risk IPI was 23% to 27% in E4494 compared with 12% to 15% in the GELA study. Median follow-up at time of last presentation of E4494 was 3.5 years. Response rates in this study did not differ by treatment arm; this may have been an artifact of the response definition or related to the schedule of rituximab. Time-to-treatment failure (TTF) at 3 years favored R-CHOP (53%) versus CHOP (46%; \(P = .04\)). Maintenance rituximab significantly prolonged the TTF (\(P = .009\)); however, the prolongation in TTF with rituximab maintenance was limited to CHOP (\(P = .0004\)) and not seen after R-CHOP (\(P = .81\)). No significant differences in OS according to induction therapy or maintenance therapies were observed. However, in an analysis in which patients who received maintenance rituximab were removed, an advantage to R-CHOP was observed for both TTF and OS.

Other results in the literature may guide the design of future therapeutics in older patients. Patients in the age range of 60 to 65 years may benefit from dose-dense or dose-intense regimens akin to younger patients.8 In a trial comparing eight cycles of CHOP with ACVBP plus sequential consolidation, the 5-year EFS was 39% in the ACVBP group and 29% in the CHOP group (\(P = .005\)). The OS at 5 years was also significantly longer for patients treated with ACVBP: 46% compared with 38% for patients treated with CHOP (\(P = .036\)). However, it appears that ACVBP cannot be used in patients older than 65 years because of its toxicity. A German study has also shown improvement over classical CHOP (CHOP administered every 3 weeks [CHOP-21]) when the CHOP regimen was administered every 2 weeks (CHOP-14) in patients age > 60 years.9 The conclusions from these studies, employing regimens associated with greater toxicity and expense, must now be reconsidered as their additional benefit when rituximab is added to standard chemotherapy remains unproven.

Given that current treatment is not satisfactory for poor-risk patients, GELA is testing whether administering R-CHOP every 2 weeks might increase the response rate and prolong the response duration in these patients. GELA is also testing whether maintaining a hemoglobin level at 13 g/dL in these patients may render them better able to tolerate the dose-dense regimen.
Young Patients With Intermediate-Risk DLBCL

According to the aa-IPI, these patients have one adverse prognostic factor, usually advanced stage or high LDH. The MInT study led by the German Lymphoma Group showed that R-CHOP or R-CHOP–like regimens were superior to the same chemotherapy without rituximab in young patients with favorable or intermediate-risk disease. In this trial, 57% patients had an aa-IPI score of 1. After a median follow-up of 22 months, patients receiving the R-CHOP–like regimen had a significantly longer TTF (P < .00001), with estimated 2-year TTF rates of 60% (CHOP-like) compared with 76% (R-CHOP–like). Similarly, OS was significantly different (P < .001), with 2-year survival rates of 87% (CHOP-like) and 94% (R-CHOP–like), respectively. However, 2-year TTF after the R-CHOP–like regimen in patients with bulky disease and/or an aa-IPI score of 1 was significantly worse (P < .001) than in patients with aa-IPI of 0 and no bulk (71% v 90%, respectively).

Is it possible to achieve survival greater than the 60% to 70% at 10 years? HDT with autologous transplant has not shown any benefit in subgroup analyses of randomized trials. To date, no prospective randomized study has concluded that a dose-dense or dose-intense regimen performs better than CHOP or R-CHOP in this group of patients. Currently, GELA is comparing R-CHOP to R-ACVBP for treating the group of patients with an aa-IPI score of 1.

Young Patients With Poor-Risk DLBCL

Young patients with poor-risk DLBCL, defined by an aa-IPI score of 2 or 3 and age younger than 60 years, are characterized by truly refractory disease, evidenced by progression during or early after treatment, or later relapse. Attempts to modify treatment to improve the response rate and reduce the proportion of patients with progressive disease have been unsuccessful to date: the best CR rate is currently around 65%. In contrast, some but not all attempts to decrease the relapse rate by consolidation with HDT have succeeded. Two of the positive studies include the GELA LNH-87.2 study that compared the standard consolidation with sequential chemotherapy with HDT and autologous transplantation after four cycles of ACVBP. With a median follow-up of 8 years, HDT was superior to sequential chemotherapy; DFS rates of 55% (95% CI, 46% to 64%) and 39% (95% CI, 30% to 48%), respectively. The 8-year OS rate was significantly superior in the HDT arm (64%) compared with the sequential chemotherapy arm (49%). Building on prior results, GELA is currently testing the hypotheses that rituximab added to ACVBP may improve the response rate and the addition of rituximab maintenance after HDT and transplantation may reduce the relapse rate.

A second HDT study with positive results, in which patients with high-risk disease were excluded, also comes from France. On the basis of these data, HDT with autologous transplantation may be considered for selected patients who achieve CR with a dose-intense and/or dose-dense regimen. However, the role of HDT and transplantation in this setting has been challenged by a recent meta-analysis. The current US Intergroup study (S9704), which is assessing the role of HDT and autologous transplantation after five cycles of R-CHOP versus completion of eight total cycles in younger patients with high-intermediate or high-risk disease, should further inform this debate.

Very Old Patients With DLBCL

Patients older than 80 years represent a growing DLBCL group. Most are able to receive life-prolonging treatment, but conventional treatments may not be feasible due to comorbid conditions and inadequate marrow reserve. Relatively few prospective studies have specifically addressed this group of patients. GELA is currently conducting a study with “adapted” R-CHOP in these patients. Adapted means that doses of doxorubicin, cyclophosphamide, and vincristine are reduced for the first cycle (25 mg/m², 400 mg/m², and 1 mg/m², respectively) and may be increased for further cycles if the tolerance is good. In combination with rituximab, it appears feasible to strive for a treatment response that may prolong the survival of these patients without undue toxicity.

CONCLUSION

During the last 20 years, the outcome for patients with DLBCL has significantly improved. Major improvements were (1) the addition of rituximab to combination chemotherapy with higher response rates and lower relapse rates; (2) the intensification with high-dose therapy for patients relapsed after conventional treatment and for selected high-risk patients as primary treatment; and (3) the description of benefit associated with dose-dense and dose-intense regimens. There continues to be room for improvement, however, particularly in those with higher-risk disease, the elderly, and patients with disease that is initially insensitive to rituximab-chemotherapy.

Advances in these areas and a more individualized approach to therapy will likely emerge from better understanding of the pathogenesis of DLBCL. As a step in that direction, the DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) regimen plus rituximab developed by Wilson et al is being compared with R-CHOP in a CALGB phase III trial that will also incorporate molecular profiling and pharmacogenomics. Studies such as these with strong biologic underpinnings, together with the discovery of new targets and evaluation of novel therapeutics, will be required to further advance the treatment of DLBCL.
Diffuse Large B-Cell Lymphoma

Author’s Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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