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# Treatment of Diffuse Large B Cell Lymphoma

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Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma in all countries and all age groups. DLBCL is potentially curable, and the outcome of patients with DLBCL has completely changed with the introduction of therapy involving the monoclonal antibody rituximab in combination with chemotherapy. Nonetheless, relapse is detected after treatment with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone in approximately 30% of patients. It has recently become clear that DLBCL represents a heterogeneous admixture of quite different entities. Gene expression profiling has uncovered DLBCL subtypes that have distinct clinical behaviors and prognoses; however, incorporation of this information into treatment algorithms awaits further investigation. Future approaches to DLBCL treatment will use this new genetic information to identify potential biomarkers for prognosis and targets for treatment.

**Keywords:** Diffuse large B cell lymphoma; Therapeutics; Rituximab; Stem cell transplantation

## INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults and the most frequent subtype of non-Hodgkin lymphoma (NHL) in all countries around the world and every age group [1,2]. DLBCL is found most commonly in people who are middle-aged or elderly, with the median age at diagnosis of DLBCL in the sixth decade, and men are slightly more likely to develop DLBCL than women. Despite being classified as a single disease entity by the World Health Organization [2], DLBCL is a remarkably heterogeneous disease with considerable variation in clinical behavior, response to therapy, and long-term outcome (Fig. 1). Recent studies involving gene expression microarray analysis of DLBCL have revealed significant heterogeneity within this diagnosis [3]. The International Prognostic Index (IPI), which includes five parameters (age, performance status, stage, lactate dehydrogenase level,

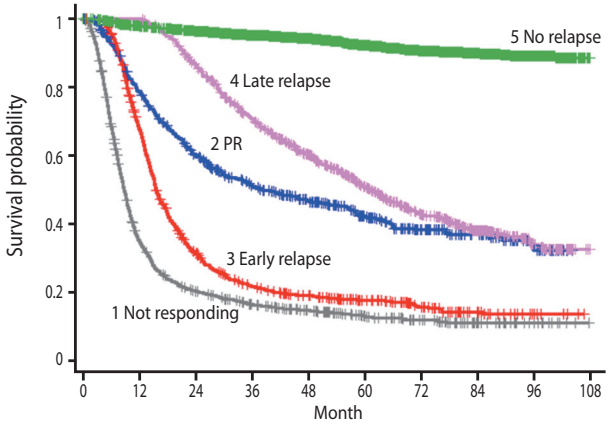


**Figure 1.** Outcome according to response to first treatment in patients with diffuse large B cell lymphoma (based on GELA database; Courtesy of Bertrand Coiffier, Hospices Civils de Lyon, Lyon, France).

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and extranodal site involvement), is the most commonly used means of risk stratification in DLBCL and has been further validated in the rituximab era [4]. The IPI score is used routinely to identify patients with high-risk disease. However, within the low or low-intermediate IPI group, there currently is no reliable way of prospectively identifying the subset of patients destined to do poorly, in terms of either primary refractory disease or an early relapse. Patients with identical IPI scores may exhibit striking variability in outcome, suggesting the presence of significant heterogeneity within each IPI category.

To predict the prognosis of patients with DLBCL at diagnosis, recent studies have examined the molecular origin of DLBCL to identify markers that stratify DLBCL cases based on the cell of origin [3,5-9]. Recent attempts using gene expression profiling (GEP) or immunohistochemical (IHC) markers to identify the cell of origin in DLBCL or the activation/suppression of signaling pathways are likely to be more successful in increasing our understanding of the biology of DLBCL and predicting the response to therapy and prognosis than the standard morphologic and clinical criteria used to date [10]. GEP has revealed that DLBCL consists of at least three major subtypes derived from B cells at different states of differentiation and with unique molecular pathogenesis: germinal center B cells (GCBs), activated B cells (ABCs), and primary mediastinal B cells.

DLBCL is typically treated with combination chemoimmunotherapy that includes the antibody rituximab and anthracyclines [11-15]. Various regimens cure approximately 60% to 70% of patients with DLBCL [4]; however, some patients either fail to respond to rituximab-based therapy or relapse early, or experience a poor outcome with second-line or salvage therapies.

## FRONT-LINE TREATMENT

Common treatment algorithms for the management of DLBCL are divided into strategies for localized disease (Ann Arbor stages I and II) and advanced-stage disease (stages III and IV). Until recently, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone (CHOP) chemotherapy administered every 21 days (CHOP21) remained the standard therapy for DLBCL, with a long-term overall survival (OS) rate of approximately 40% [16].

In the 1980s, several studies were performed using aggressive combination-chemotherapy regimens such as MACOP-B and ProMACE-CytaBOM in an attempt to improve the results of DLBCL treatment but these programs were costly, difficult to administer, and appeared to be more toxic than CHOP [17-19]. The Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG) initiated a prospective, randomized, phase III trial that compared CHOP with three aggressive multi-agent regimens [16]. When compared with these intensive chemotherapy regimens, the standard CHOP regimen produced similar survival outcomes in patients with advanced NHL. However, fatal toxic reactions were less common in patients treated with CHOP, thus establishing CHOP as the standard of care for patients with DLBCL. This finding has been confirmed by other trials comparing more aggressive chemotherapy regimens with standard CHOP therapy [20,21]. Several trials have subsequently explored modifications of the CHOP regimen based on dose-intensity and dose-density in an attempt to improve its efficacy [22-24].

In 1997, rituximab became the first monoclonal antibody approved for use by the Food and Drug Administration for follicular lymphoma, and this immunotherapy was soon applied to DLBCL and other B-cell NHLs [25]. Rituximab is an antibody directed against the CD20 protein, which is primarily found on the surface of B cells and is present on many lymphoma cells. Although the mechanism is not completely understood, rituximab is thought to induce lysis of lymphoma cells through complement-mediated cytolysis, antibody-dependent cell cytotoxicity, and direct induction of apoptosis. In addition, rituximab acts synergistically with chemotherapy [26].

Rituximab significantly improves treatment outcome in DLBCL. A large randomized phase III study demonstrated improved OS in patients with DLBCL who were treated with rituximab with CHOP (R-CHOP) therapy [27]. Other studies showed that combined rituximab and chemotherapy clearly prolonged event-free survival (EFS) and OS in elderly patients [12,15]. The MabThera International Trial Group study compared a CHOP-like chemotherapy regimen and the same regimen with the addition of rituximab in patients under 60 years of

age with good prognosis and demonstrated prolonged EFS and OS in the rituximab-treated group [14]. Based on the results of these clinical trials, R-CHOP therapy is now considered to be the 'standard therapy' in DLBCL, especially for young low-risk and elderly DLBCL patients. However, it has not yet provided a satisfactory outcome in patients in the high-risk group according to IPI classification.

## DIFFERENT TREATMENT STRATEGIES FOR DIFFERENT STAGES OF DISEASE

The benefit of 3 cycles of CHOP followed by involved field radiotherapy (IFRT) (5-year-OS of 95%) in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors) was confirmed in a series from the British Columbia Cancer Agency [28]. The ECOG 1484 study showed that the addition of IFRT to CHOP (eight cycles) prolonged disease free survival (DFS) in patients with limited-stage DLBCL who had achieved complete remission (CR) compared with CHOP alone (6-year-DFS 73% for IFRT plus CHOP vs. 56% for CHOP alone) [29]. However, in the GELA LNH 93-4 study, the addition of radiotherapy to four cycles of CHOP did not provide any advantage over four cycles of CHOP alone for the treatment of elderly patients with low-risk localized aggressive lymphoma.

In the SWOG 0014 study, the addition of rituximab to CHOP (three cycles) and IFRT showed efficacy in patients with limited-stage DLBCL. In historical comparison, these results were better than those for patients treated without rituximab. R-CHOP (three cycles) with IFRT or R-CHOP (six cycles) with or without IFRT was recommended for patients with non-bulky (less than 10 cm) DLBCL [30].

R-CHOP21 chemotherapy has been the standard treatment for patients with advanced stage DLBCL based on results of the GELA study demonstrating that the addition of rituximab to CHOP21 improved progression-free survival (PFS) and OS in elderly patients with advanced DLBCL [11,16,31]. These findings have been confirmed in additional randomized trials [12,32].

Prior to the introduction of rituximab, six cycles of dose dense CHOP (CHOP14) as first-line therapy was found to be superior to six cycles of CHOP21 in patients older than 60 years [23]. In the RICOVER 60 trial, the addition of rituximab to six or eight cycles of CHOP14 (R-CHOP14) improved clinical outcomes in elderly patients compared with CHOP14 alone [13,33]. Over a median observation time of 82 months, both EFS and OS were significantly improved after R-CHOP14 [33]. Ongoing randomized studies are evaluating the role of R-CHOP14 versus R-CHOP21 [34,35]. Although randomized trials have found the French ACVBP-R regimen to be superior to R-CHOP in younger patients, toxicity precludes its use in older patients [36,37].

Dose-adjusted (DA) R-EPOCH has shown significant activity in untreated patients with DLBCL [34,38], and an ongoing phase III randomized trial is evaluating DA R-EPOCH versus R-CHOP in untreated patients with DLBCL.

## DIFFERENT TREATMENT STRATEGIES FOR GCB AND ABC DLBCL SUBTYPES

To segregate DLBCL into biologically meaningful subgroups that might allow identification of rational therapeutic targets, the Leukemia and Lymphoma Molecular Profiling Project began gene expression analysis of DLBCL biopsy samples using DNA microarrays and identified biologically distinct and prognostically meaningful molecular subgroups of DLBCL [8]. Recent gene expression microarray analyses of DLBCL have revealed significant heterogeneity within this diagnosis [3]. For example, GCB and ABC DLBCL subtypes are derived from B cells at different stages of differentiation. GCB DLBCL appears to arise from GCBs, whereas ABC DLBCL likely arises from post-GCBs that are blocked during plasmacytic differentiation [39].

Analysis of molecular subtype and outcome following upfront CHOP treatment shows a statistically significant difference in 5-year-OS of the DLBCL subtypes: 59% for GCB DLBCL and 31% for ABC DLBCL, independent of IPI risk group [3,40]. Because this analysis was performed on biopsies obtained in the pre-rituximab era, a second analysis was performed on 233 biopsies obtained from patients treated with R-CHOP [39]. Similarly, patients with GCB DLBCL had a more favorable survival than those with ABC DLBCL, with 3-year-OS rates of 84% and 56%, respectively ($p < 0.001$), and, as

expected, the OS of both GCB and ABC DLBCL was better than in the pre-rituximab era.

GEP is not yet popular for routine clinical use. In its place, investigators have developed IHC models, and immunostaining algorithms have been used to differentiate between these two subtypes using combinations of CD10, BCL6, IRF4/MUM1, GCET1, and FOXP1 [41,42]. Despite variable reproducibility, these approaches have successfully distinguished GCB from non-GCB DLBCL in a number of clinical trials [5,6,43].

Although the technology of IHC is more established than that of GEP it is not without standardization and reproducibility issues, highlighting the fact that even apparently simplified approaches have limitations and are not always reliable [44,45]. Recent comparative analysis revealed that the rate of misclassification using IHC is high, especially for GCB subtypes, ranging from 30% to 60% [46]. This study also showed that GEP successfully predicted PFS and OS based upon GCB versus ABC subtypes, whereas none of the five IHC algorithms was able to do so. Attempts to adopt IHC surrogates for GEP findings have met with only modest and controversial success.

It is not necessary to perform any kind of genetic testing to render a diagnosis of DLBCL. However, it is clear that genetic factors and/or the cell of origin are key determinants of specific subtypes and prognosis [45]. So far, none of the fascinating data emanating from GEP and other technologies have translated into routine clinical practice.

The contemporary relevance of the role of GEP and/or the use of IHC surrogates in the rituximab era is somewhat controversial [45]. It has been proposed that BCL2-positive DLBCL benefits from the addition of rituximab to CHOP chemotherapy, whereas BCL2-negative cases do not [47]. Other studies suggest that the addition of rituximab to CHOP benefits BCL6-negative DLBCL, but not BCL6-positive cases [48]. It therefore appears that patients with ABC DLBCL benefit from the addition of rituximab, but those with GCB DBLCL do not. Some reports suggest that the use of rituximab eliminates the prognostic differences between these two groups [48-50] although other studies do not support this notion.

Even though GCB DLBCL has a better prognosis than ABC DLBCL, more than of 30% of patients are not cured. BCL6 is an important modulator of B cell development in the germinal center, and mutations/translocations in BCL6 enhance its inhibitory effects on apoptotic stress responses and promote proliferation, both of which are associated with treatment failure [51-55]. An interesting and potentially important observation is the effect of topoisomerase II inhibition on BCL6 expression through ubiquitin-mediated protein degradation and possibly transcriptional inhibition [56]. The German high-grade lymphoma study group showed that addition of the topoisomerase II inhibitor etoposide to CHOP (CHOEP) significantly improved the EFS of younger, but not older, patients with untreated DLBCL [23,24]. The higher frequency of GCB DLBCL in younger patients may explain why the benefit of etoposide was only found in patients under 60 years and not in older patients.

Interestingly, the positive effect of including etoposide in CHOEP was lost when rituximab was also added (R-CHOEP) [23]. This may reflect the overall salutary effect of rituximab on the outcome of both GCB and ABC DLBCL, rather than a specific effect on BCL6. In this regard, the DA-EPOCH-R regimen, which was designed to inhibit topoisomerase II, might be particularly effective in GCB DLBCL, in part due to its effective inhibition of topoisomerase II and BCL6.

ABC DLBCL is characterized by the expression of genes associated with survival and proliferation and has an inferior clinical outcome. Based on *in vitro* evidence that the proteasome inhibitor bortezomib blocked degradation of phosphorylated inhibitor of kappa B and consequently inhibited nuclear factor-kappa B activity in ABC DLBCL cell lines, bortezomib was combined with DA-EPOCH in patients with relapsed/refractory DLBCL [57-59]. Bortezomib alone had no activity against DLBCL, but when combined with chemotherapy demonstrated a significantly higher response and median OS in ABC DLBCL than in GCB DLBCL (response, 83% vs. 13%; $p = 0.0004$ and OS, 10.38 months vs. 3.4 months; $p = 0.0026$). These results suggest that bortezomib enhances the effectiveness of chemotherapy in ABC, but not GCB DLBCL, and provide a rational therapeutic approach based on genetically distinct DLBCL subtypes [60]. When bortezomib was combined with R-CHOP in patients with previously untreated DLBCL to assess its toxicity and efficacy [60], there was no

difference between patients with GCB and ABC DLBCL, suggesting that bortezomib overcame the adverse prognostic effect of the ABC DLBCL subtype. Based on these studies, a randomized study of R-CHOP + bortezomib in untreated patients with ABC DLBCL is ongoing (Pyramid study).

A recent study suggesting that lenalidomide may be preferentially effective in ABC DLBCL [61] also warrants further investigation.

## SALVAGE TREATMENT FOR PATIENTS WITH RELAPSED DLBCL

Although the adoption of R-CHOP as the new standard of care has improved outcomes for DLBCL, many patients still relapse. In such cases, the standard approach for fit patients with DLBCL has been to proceed toward salvage therapy and consolidation with autologous stem cell transplantation (ASCT).

The 1995 PARMA trial is the only randomized trial comparing ASCT versus salvage chemotherapy [62]. This study reported a significantly superior OS and EFS in patients who underwent salvage ASCT. Based on this study, ASCT has become the standard of care in patients less than 60 years old with chemosensitive relapsed or primary refractory aggressive NHL.

Several regimens exist for salvage lymphoma therapy including ifosphamide, carboplatin, etoposide (ICE), etoposide, methy prednisolone, high-dose cytarabine, cisplatin (ESHAP), dexamethasone, cisplatin, cytarabine (DHAP), and dexamethasone, cisplatin, gemcitabine. These regimens have various response rates. Although the standard of salvage therapy is still being debated, the addition of rituximab to the salvage regimen appears to benefit relapsed patients, especially those previously unexposed to rituximab. The Hemato-Oncologie voor Volwassenen Nederland group randomized relapsed patients to DHAP with or without rituximab. After two cycles, 75% of the patients in the rituximab with DHAP (R-DHAP) arm had responsive disease compared with 54% in the DHAP arm ($p = 0.01$). 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 [63]. Moreover, rituximab does not appear to impair stem cell engraftment or adversely affect transplantation toxicity and is associated with improved PFS when administered before ASCT for DLBCL [64].

One study conducted a retrospective review of patients treated with rituximab with ICE (R-ICE) and compared them with historical controls treated with ICE alone. R-ICE given for three cycles produced a CR in 53% of patients, and none of the patients had treatment-related toxicity that precluded ASCT [65]. It is important to note that patients in both studies had received prior induction chemotherapy without rituximab.

Another study showed that among patients with relapsed or refractory DLBCL who received rituximab with ESHAP as salvage therapy with curative intent, those previously exposed to rituximab had very low CR and overall response rates [66]. The most effective regimen for salvage chemotherapy after R-CHOP failure was addressed by a prospective multicenter phase III study Collaborative Trial in Relapsed Aggressive Lymphoma [67,68], in which DLBCL patients were randomized to receive salvage R-ICE or R-DHAP. After three courses, responders underwent high-dose therapy, and ASCT. There was no statistical difference between R-ICE and R-DHAP in overall response rate (63.5% vs. 62.8%), 3-year-PFS (31% vs. 42%), and 3-year-OS (47% vs. 51%), suggesting that either regimen can be used for salvage therapy. Because nearly all patients with DLBCL currently receive front-line R-CHOP, these data call into question our current strategies for salvage therapy, particularly for patients who relapse within 1 year of initial therapy.

## STEM CELL TRANSPLANTATION

The PARMA study did not enroll patients over 60 years old, and there are no comparative data for ASCT versus non-transplantation as salvage therapy in this age group. Two non-randomized studies have been published since 2000 comparing the outcomes of autologous versus myeloablative allogeneic stem cell transplantation (SCT) as treatment specifically for DLBCL patients. One study reported that allogeneic SCT patients had significantly worse 1-year-rates of OS, PFS, and treatment-related mortality (TRM) than ASCT patients, but the differences were not significant at 3 or 5

years [69]. Another study reported a significantly worse 3-year-TRM for allogeneic compared with autologous SCT patients, but no difference in survival outcomes [70]. Neither study reported a significant difference in the risk of relapse or disease progression between the two treatment groups at any time interval. One randomized study compared autologous peripheral blood SCT (PBSCT) versus bone marrow transplantation (BMT) as treatment for patients with aggressive NHL (61% with DLBCL) [71]. Patients who underwent autologous PBSCT had a significantly longer OS, but not EFS, than those who underwent autologous BMT.

A study that investigated the impact of three courses of intensified CHOP versus no CHOP prior to two cycles of induction followed by first-line ASCT for patients with de novo aggressive NHL found that patients who received intensified CHOP had significantly better OS and EFS than those who did not [72].

## CONCLUSIONS

DLBCL is a clinically and biologically diverse disease that cannot easily be subdivided into distinct disease entities because of overlapping morphology and pathogenetic features. Currently there are no reliable markers to prospectively identify patients in each subgroup. R-CHOP is the standard therapy in elderly and low-risk young patients. As we better understand the biological explanation for this heterogeneity, we hope to develop more specific and more effective therapies for high-risk patients. The ultimate aim is to improve the outcome of patients with DLBCL through the selection of individualized treatment regimens.

### Conflict of interest

No potential conflict of interest relevant to this article is reported.

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