Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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Despite overall improvements in outcomes of diffuse large B-cell lymphoma (DLBCL), approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of morbidity and mortality. Novel insights from gene-expression analyses have increased our understanding of chemotherapy resistance and yielded rational targets for therapeutic intervention to both prevent and treat relapsed/refractory DLBCL. The clinical approach to relapsed/refractory DLBCL should include high-dose therapy and autologous stem cell transplantation (HD-ASCT) with curative intent in patients without comorbidities. Results from the recently reported CORAL study suggest that patients refractory to rituximab-containing regimens have inferior outcomes with HD-ASCT. Ongoing efforts to improve ASCT include novel conditioning regimens and evaluation of maintenance approaches after ASCT. Unfortunately, because the majority of patients are not eligible for ASCT due to refractory disease or age/comorbidities, these approaches have limited impact. The large group of patients not eligible for ASCT have incurable disease and should be referred for clinical trials of rationally targeted agents.

Introduction: who relapses with DLBCL?

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy in the United States. With standard therapy, including rituximab and an anthracycline-containing regimen, approximately 67% of patients in a population-based registry are alive without lymphoma with a median follow-up of 4 years.[1] Therefore, despite the improvements in overall survival (OS) of patients with DLBCL with the routine addition of rituximab therapy,[2] one-third of patients have disease that is either refractory to initial therapy or relapses after standard therapy. Although the majority of relapses occur early, a recent series has emphasized that late relapses (after 5 years) are possible, and may be associated with initial localized stage, favorable International Prognostic Index (IPI) score, and extranodal involvement at diagnosis.[3] These late relapses constituted 7% of all progressions after rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone/prednisolone (R-CHOP) or CHOP chemotherapy in a large randomized trial.

The IPI for lymphomas was developed in the 1990s and has remained the most robust clinical prognostic scheme for aggressive lymphomas since that time. In a pooled analysis, adults with aggressive nonHodgkin lymphoma (NHL, mainly DLBCL) from 16 institutions and cooperative groups in the United States, Europe, and Canada who were treated between 1982 and 1987 with combination-chemotherapy regimens containing doxorubicin were evaluated for clinical features predictive of OS and relapse-free survival. In more than 2000 patients of all ages, a derived model, based on age, tumor stage, serum lactate dehydrogenase concentration, performance status, and number of extranodal disease sites, identified 4 risk groups with predicted 5-year survival rates of 73%, 51%, 43%, and 26%.[4] These outcomes were more robust than Ann Arbor stage at predicting outcome of patients.

As therapy has changed and improved, a recent question has been whether the IPI remains predictive in the rituximab era. Sehn et al performed a retrospective analysis of a relatively small cohort of patients with DLBCL treated with R-CHOP in British Columbia to assess the value of the IPI in the era of immunochemotherapy. Redistribution of the IPI factors into a revised IPI provided a more clinically useful prediction of outcome. The "poor-risk" group still had a 4-year progression-free survival (PFS) that exceeded 50%.[5] However, a recent analysis of German clinical trials in the R-CHOP era that included $>$ 1000 patients suggested that the IPI remained prognostic in determining event-free survival (EFS), PFS, and OS.[6]

Clearly, however, these IPI factors are surrogates for biological heterogeneity among DLBCL, which leads to differential outcomes. Using gene-expression profiling, cell-of-origin studies suggested that there are at least 3 distinct subtypes of DLBCL: activated B-cell, germinal center B-cell, and primary mediastinal DLBCL.[7] Activated B-cell lymphomas have an inferior prognosis, which appears to be a more powerful predictor than the IPI in patients treated with CHOP-like regimens. Shipp et al have reported a gene-expression analysis including more than 6000 genes in diagnostic tumor specimens for patients with DLBCL treated with CHOP-based therapy.[8] These investigators applied a supervised learning prediction method to separate cured patients from patients with fatal or refractory disease. Samples from 32 patients with cured disease were compared with 26 patients with refractory disease. In this series, genes implicated in DLBCL outcome included *NOR1*, *PDE4B*, and *PKC-beta*, which regulate apoptotic responses to antigen receptor engagement. These studies suggest possible targets for therapeutic intervention.

Gene-expression profiling also provides prognostic information in the rituximab era. In an updated analysis from the lymphoma/leukemia molecular profiling project, which included tumor biopsies from 233 patients with DLBCL treated with R-CHOP, a multivariate model predicted survival.[9] The prognostically favorable "stromal-1" signature reflected extracellular matrix and histiocytic infiltration. The less favorable "stromal-2" signature appears to be an angiogenic switch, in which development of malignancy is accompanied by new blood vessel formation. Surrounding macrophages appear to contribute to angiogenesis and poor outcome in these cases, again suggesting possible targets for therapeutic intervention.

At the present time, gene-expression profiling is not available for routine clinical use. Immunohistochemistry algorithms appear to accurately determine cell of origin in the majority of cases.[10] New technology may allow more comprehensive gene-expression profiling of paraffin-embedded tissues in the near future.[11] Individual immunohistochemistry markers, including bcl-6[12] and p21,[13] appear to import prognostic information on diagnostic specimens of DLBCL treated in the rituximab era. Perhaps the most robust single marker in DLBCL is c-myc, which is present in 10%-20% of cases. Expression or amplification of c-myc results in a very poor outcome, with OS below 30% at 2 years.[14,15] Frequently, c-myc is associated with additional abnormalities, including bcl-2 translocations or overexpression, resulting in extremely poor prognosis with standard treatment.[16]

Finally, there has been enthusiasm about using response-based assessments to identify patients at risk for relapse or refractory disease. Positron emission tomography (PET) is part of routine staging and assessment of DLBCL.[17] Several investigators have explored using "early" PET imaging (after 1-3 cycles of chemotherapy) to define a high-risk group of patients likely to relapse after standard treatment. Despite the initial enthusiasm for this approach, recent data emphasize its experimental nature. For example, in a prospective trial from the Memorial Sloan-Kettering Cancer Center, patients with flurodeoxyglucose fl (FDG)-PET–positive disease after 4 cycles of R-CHOP underwent repeat biopsy, and the majority of patients with positive PET scans had negative biopsies.[18] The ECOG group revealed another major limitation in the use of interim PET scans as part of an algorithm to treat patients with DLBCL. Three independent nuclear medicine physicians involved in a prospective trial disagreed on the interpretation of interim scans approximately one-third of the time despite using consensus criteria.[19] At the present time, patients with DLBCL should not receive interim PET scans outside of a clinical trial because if a PET scan is performed, there is no clear guidance on how to proceed.[20]

Diagnosis and evaluation of the patient with relapsed or refractory disease

Given the substantial expense and morbidity of therapy and the grave prognostic impact, patients with clinical features or imaging findings consistent with relapsed disease should be evaluated with a biopsy. Whereas most of these patients will have recurrent lymphoma, other conditions (eg, sarcoid, infection, carcinoma) may be present. In addition to documenting disease, these biopsies can be informative as to current histology, because patients with DLBCL may recur at a later date with more indolent histologies such as follicular lymphoma.

Once relapse or progression is confirmed, patients should undergo a restaging evaluation that includes at minimum a complete history and physical examination, routine laboratory tests, computed tomography imaging of the chest and abdomen/pelvis, and a BM aspirate and biopsy. PET with computed tomography is often performed and may further delineate extranodal involvement. Patients with any symptoms indicative of CNS disease should undergo assessment of CNS with brain imaging and lumbar puncture for cytology and flow cytometry. Generally, CNS progressions occur during or immediately after induction therapy; late progression involving the CNS is uncommon.[21] The clinical IPI remains predictive of outcome at relapse, so these factors should be determined.[22]

Refractory disease is defined as a $< 50\%$ decrease in lesion size with induction therapy or the appearance of new lesions. Progressive or relapsed disease reflects the appearance of new lesions after attainment of complete remission. Therefore, patients who fail first-line therapy may be categorized into 3 distinct groups: (1) those relapsing after complete remission, (2) partial responders with persistent disease, and (3) refractory patients. The ultimate survival outcome is significantly different in each subgroup. True refractory patients occasionally benefit from salvage regimens but generally have a poor outlook. Partial responders will sometimes benefit from non-cross-resistant salvage regimens and might be offered high-dose therapy and autologous stem cell transplantation (HD-ASCT). Relapsed patients have the best prognosis.

The initial approach to relapsed DLBCL management is to determine whether the patient is a candidate for HD-ASCT. In the PARMA trial (Figure 1), the only randomized dataset, 215 chemotherapy-sensitive relapsed DLBCL patients were randomized to salvage chemotherapy with a cisplatinum- and cytarabine-based regimen alone or in combination with HD-ASCT.[23] Both EFS and OS were significantly superior in the transplantation group compared with the chemotherapy alone group (46% and 53% vs 12% and 32%, respectively). As suggested above, chemotherapy-sensitive patients did significantly better than those who were initially chemotherapy resistant (5-year PFS 43% vs 1-year survival of 22%). It is important to consider the strict eligibility criteria of this landmark study, which required that all patients have a complete response to an initial induction regimen with the response maintained for at least 4 weeks. Patients with CNS or BM involvement at the time of the relapse were excluded.

There are no randomized data on eligibility for aggressive HD-ASCT. With improvements in supportive care, including routine use of hematopoietic growth factors, mortality after this procedure has decreased to $< 5\%$ in most experienced institutions. A recent review of the criteria used to choose patients for allogeneic transplantation is appropriate for variables used to consider patients who are eligible for autologous transplantation.[24] Commonly used exclusion criteria include advanced age (above 70-75 years in most transplantation centers), comorbidities including severe pulmonary compromise or impaired left ventricular dysfunction, and inadequate social support to assist in care after transplantation. An analysis of "elderly" patients in the European BM transplantation registry (median age only 63) suggests increased treatment-related mortality and decreased disease control in older patients receiving HD-ASCT for relapsed DLBCL.[25] Although it is clear that functional age may be more predictive than biological age, older patients are less likely to benefit from the procedure and more likely to have higher-risk disease features. Another recent study of ASCT after carmustine, etoposide, cytarabine, melphalan (BEAM) conditioning was efficacious and well tolerated in a cohort of patients over the age of 60 with DLBCL. In this study, age alone did not predict treatment-related mortality or disease outcome; rather, a comorbidity index score was highly predictive.[26] This study only evaluated patients who were felt to be eligible to proceed with HD-ASCT because they had preserved performance status and acceptable cardiac, pulmonary, hepatic, and renal function. Therefore, the decision on whether a patient with relapsed lymphoma is eligible for an aggressive approach should be individualized and the threshold should be kept low to refer a patient to a transplantation center for evaluation.

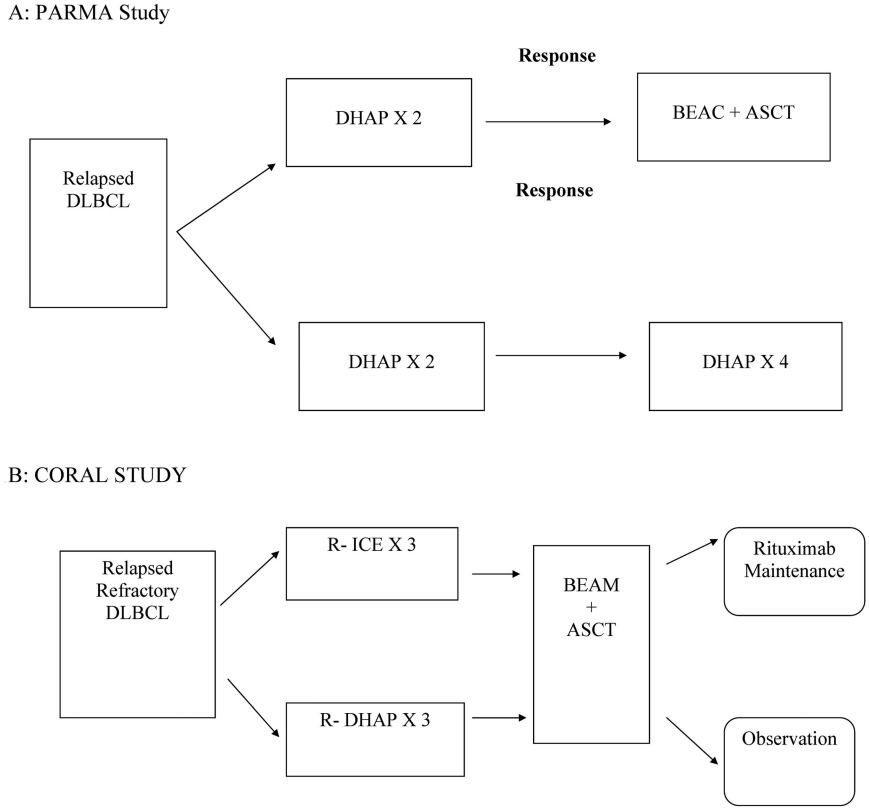

Figure 1. PARMA and CORAL study schemas.

Clinical approach to patients eligible for ASCT in the rituximab era

Salvage Therapy

The first goal in patients who are ultimately eligible for HD-ASCT is to administer a non-cross-resistant salvage regimen, generally including high doses of chemotherapy. The main goal of this treatment is to minimize the disease burden and demonstrate continued chemosensitivity. Numerous studies have emphasized the importance of demonstrating chemosensitivity before HD-ASCT. Complete remission is not required, but demonstration of response is the most predictive factor of ultimate outcome after HD-ASCT. Indeed, the best outcomes of HD-ASCT have been reported in patients who are negative on FDG-PET imaging before HD-ASCT.[27]

The outcome of salvage therapy has changed in the rituximab era. For example, Martin et al reported the results of the GEL/TAMO study, which evaluated the influence of prior rituximab use in response rates of rituximab plus etoposide, methylprednisolone, cytarabine, cisplatin (R-ESHAP) as salvage therapy for patients with relapsed or refractory DLBCL. In this retrospective analysis, 163 patients with relapsed or refractory DLBCL who received R-ESHAP with curative intent were analyzed. Patients were stratified according to whether rituximab had been administered previously and during induction therapy or not.[28] Prior exposure to rituximab was an independent adverse prognostic factor of both PFS and OS.

Other investigators, including the HOVON group and the MKSCC group, have shown improved response rates by adding rituximab to salvage regimens such as dexamethasone, Ara-C, and cisplatin (DHAP) and ifosfamide, carboplatin, etoposide (ICE), but the majority of the patients in these earlier studies had not been previously exposed to rituximab.[29,30] The analysis of long-term follow-up of patients relapsing after the GELA study of R-CHOP versus CHOP in previously untreated patients 60-80 years of age with DLBCL showed that patients treated with a rituximab-containing salvage regimen had a 2-year survival of 58% compared with 24% for those treated without rituximab ($P = .00067$).[31] However, in the CHOP arm, the benefit of the addition of rituximab at time of salvage therapy was statistically significant ($P = .002$), whereas in the R-CHOP arm it was not ($P = .23$).

The recently completed multicenter phase 2 CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study aims to further guide the choice of salvage chemotherapy in DLBCL and to assess the role of rituximab maintenance after HD-ASCT (Figure 1).[32] This report is the most important dataset defining outcomes of HD-ASCT in the rituximab era. Patients with relapsed DLBCL or patients who had not achieved a complete response after CHOP or R-CHOP therapy were first randomized between ICE and DHAP, both combined with rituximab (R-ICE or R-DHAP). Patients were stratified on the basis of prior exposure to rituximab, relapsed versus refractory disease, and relapse less than or greater than 12 months from front-line therapy. After 3 courses, responders were treated by ASCT after BEAM conditioning. A second randomization then allocated patients to maintenance treatment with rituximab or to observation. The recently published analysis of the first question revealed no significant difference between R-DHAP and R-ICE as salvage therapy; the response rate of both regimens was 63%.[32] Therefore, more than one-third of patients did not respond to salvage therapy, and only one-half were able to proceed to HD-ASCT. In addition, there was no difference in EFS or OS

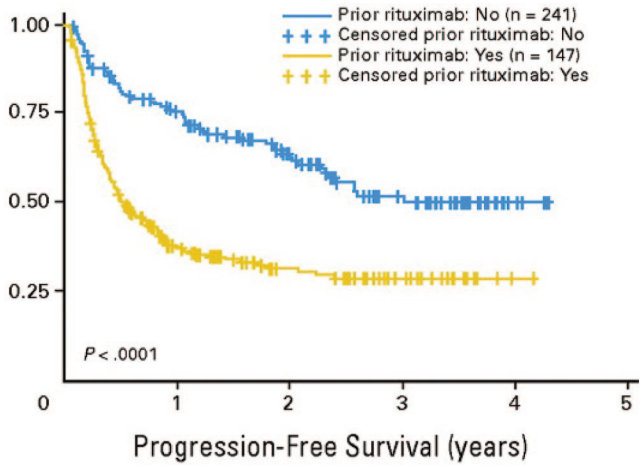

Figure 2. CORAL study results. PFS of patients in CORAL study according to prior exposure to rituximab. Patients receiving rituximab as part of induction therapy had inferior outcome. Reproduced with permission from the *Journal of Clinical Oncology*.[32]

between R-DHAP–treated patients and R-ICE–treated patients. Stem-cell collections were similar in both groups. This dataset underscored the point that there is no clear superior salvage regimen. Because the drug costs of R-DHAP are significantly less than R-ICE, R-DHAP is preferred as a first-line salvage therapy.

A key finding within the first CORAL analysis was that the response rate to salvage therapy was lower in patients previously treated with rituximab compared with rituximab-naive patients (83% vs 51%; $P < .001$; Figure 2). This difference translated to ultimate outcome: the 3-year EFS was significantly affected by prior rituximab treatment compared with no prior rituximab (21% vs 47%). Patients in the CORAL study who had early progression (< 1 year) after induction therapy also had poor outcome; there were more of these patients in the group previously exposed to rituximab. These results have been confirmed by several other single institutional experiences.[33,34] One key question is whether patients refractory to a rituximab-containing regimen should be retreated with rituximab. Although there are no clear data to suggest benefit, rituximab should be given in this situation due to low morbidity and the potential for synergy with chemotherapy.[35]

For patients who do not respond to the first salvage regimen, the outcome is extremely poor. Although many clinicians attempt a second-line salvage regimen in this setting, the ultimate curability of these patients is quite limited, and they should be considered for clinical trials of novel agents. In a series of 74 patients from Cornell University with relapsed or refractory DLBCL who underwent second-line chemotherapy, 27 (36%) did not respond; a proportion similar to the CORAL study.[36] The median OS of nonresponding patients was only 4 months, and only 1 patient (4%) survived for 1 year. The choice of third-line aggressive chemotherapy instead of less-intensive approaches did not confer a survival benefit, emphasizing the poor outcome of this group and the lack of utility of second-line salvage therapy.

High-dose therapy and ASCT

There is no "standard" conditioning regimen for HD-ASCT support. Commonly used myeloablative regimens include BEAM, cyclophosphamide, carmustine, etoposide (CBV), and cyclophosphamide/total body irradiation (TBI). Although there have been no randomized studies, comparative studies suggest lower rates of secondary myelodysplastic syndrome/acute myeloid leukemia and other long-term toxicities when chemotherapy-only conditioning regimens are used.[37] For this reason, many favor either the BEAM or CBV regimen as a standard approach, with the possible addition of localized radiation therapy in sites of persistent disease.[38]

A major focus over the past several years to improving standard conditioning has been the incorporation of radioimmunotherapy (RIT). RIT represents a rational alterative to TBI, providing targeted radiotherapy before transplantation while sparing normal structures. Press et al reported the use of I^{131} tositumomab combined with etoposide and cyclophosphamide followed by stem cell rescue in patients with relapsed NHL as part of a phase 1/2 clinical trial.[39] Overall toxicities were similar to traditional conditioning regimens using TBI; however, on historical comparison there were fewer deaths with the I^{131} tositumomab regimen (17.6% vs 7.6%). When historically compared with traditional conditioning with TBI/etoposide/cyclophosphamide, there was a significant improvement in OS and PFS after transplantation.

Given the effectiveness of high-dose RIT as a conditioning regimen, standard dose RIT has also been used combined with standard high-dose chemotherapy before ASCT in lieu of TBI. Vose et al reported the results of a phase 1 clinical trial using standard BEAM with outpatient I^{131} tositumomab.[40] Twenty-three patients with refractory or relapsed $CD20^+$ NHL were enrolled; 48% had primary refractory disease. The 3-year OS rate was 55%. Toxicity was similar to BEAM alone. In another RIT regimen, Nademanee et al reported on 31 patients with advanced-stage NHL who were treated with ibritumomab tiuxetan, cyclophosphamide, and etoposide conditioning.[41] Two-year OS was estimated at 92%, with a relapse-free survival of 78% at the 22-month follow-up. Toxicity was similar compared with historical controls using traditional regimens.

Based upon these favorable results, the BMT Clinical Trials Network has completed a randomized trial comparing BEAM plus rituximab with BEAM plus I^{131} tositumomab as conditioning in patients with relapsed DLBCL. The results of this study are eagerly awaited. Until this trial has been presented, the incorporation of RIT into conditioning should be considered experimental, and only done in the context of a clinical trial.

The other key investigational strategy to improving outcome after HD-ASCT in patients with relapsed DLBCL has been to incorporate therapies after transplantation that are designed to maintain remission. The aforementioned CORAL study is evaluating the role of rituximab maintenance in this setting based on data in follicular lymphoma confirming a PFS advantage to rituximab maintenance after ASCT. Prolonged cytopenias and increased infections have been reported with this strategy,[42] so it is not recommended outside of clinical trials until the results of the CORAL study are finalized. The preliminary analysis of the CORAL study failed to show a benefit to rituximab in this maintenance setting. Other agents currently under study as maintenance include lenalidomide, bortezomib, and vorinostat.

Despite these efforts, improving HD-ASCT will only have a limited impact on the outcome of patients with relapsed or refractory DLBCL (Figure 3). To affect the majority of patients, future efforts should include improving salvage therapy by including novel agents

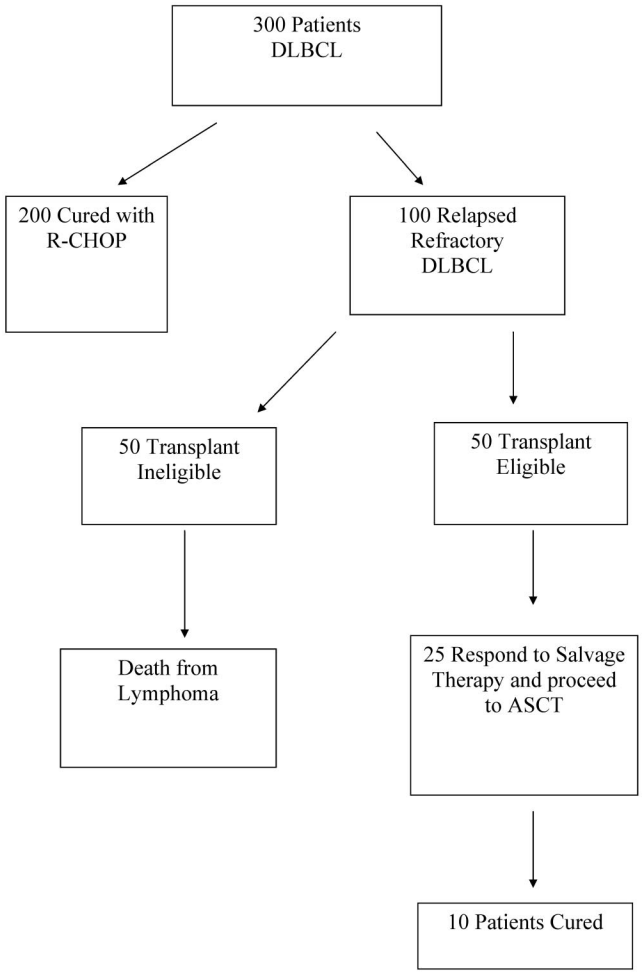

Figure 3. Limited benefit of ASCT for relapsed DLBCL. In the rituximab era, the ultimate benefit of HD-ASCT is limited. For 300 patients diagnosed with DLBCL, 200 will be cured with up-front therapy. Of the 100 who relapse, at least half are unlikely to be eligible for aggressive approaches due to advanced age, comorbidities, social and access issues, or individual choice. Therefore, only 50 of these patients can be approached with curative intent. Based on the results of CORAL study, because these patients have had previous rituximab exposure, the response rate to salvage therapy is only 51%; therefore, at most, 25 patients will undergo ASCT. The 3-year PFS of those treated with ASCT is 40%, so only 10 patients of the original 300 de novo patients or the 100 relapsed patients are ultimately cured of lymphoma with HD-ASCT.

and improving the outcome of the large group of patients not eligible for ASCT.

Relapse after HD-ASCT

The prognosis of the majority of patients who relapse after HD-ASCT is very poor. A historical series suggested that the median survival of a patient who relapses after HD-ASCT is only 3 months, and although a few patients can enjoy durable remissions, the majority succumb to lymphoma very quickly after relapse.[43] Because many of these patients are young and otherwise healthy (due to their eligibility for HD-ASCT), there has been enthusiasm to pursue allogeneic stem-cell transplantation (alloSCT) in this setting. Historically, the results of alloSCT have been disappointing, with high treatment-related mortality and limited disease control.[44] Recently, an analysis of the European Group for Blood and Marrow Transplantation database was performed of patients receiving alloSCT after failing HD-ASCT for DLBCL.[45] This study included 101 patients; conditioning regimens were nonmyeloablative in 64 patients. The 3-year PFS was 41% and OS was 53%. Patients with long remissions after ASCT and with sensitive disease before alloSCT had the best outcome. This series suggests that in highly selected patients with relapsed DLBCL (an international registry experience of 9 years with only 101 patients), there is a possible role for alloSCT and the associated GVL effect when HD-ASCT fails.

Therapy of relapsed DLBCL in patients not eligible for HD-ASCT

The outcome of this large group of patients is very poor, with essentially no chance at prolonged control of disease. Attempts at conventional salvage regimens in this population of generally older patients do not result in disease control and have substantial morbidity.[46] Therefore, goals of therapy in this setting are purely palliative, and toxicities of treatment need to be considered given their limited benefit. For this reason, in this population of patients, single-agent therapies, often in combination with rituximab, should be used. Single-agent rituximab has modest, generally transient activity in this setting. Other well-tolerated agents include gemcitabine or components of salvage regimens such as high-dose cytarabine. Other investigators have combined oral agents in a low-dose chemotherapy program ("metronomic chemotherapy") with evidence of responses.[47] Localized radiation therapy can be palliative if large masses are symptomatic. Lenalidomide, an approved immunomodulatory agent for multiple myeloma and myelodysplastic syndromes, has significant single-agent activity in this setting. A phase 2 trial of relapsed aggressive lymphoma including DLBCL demonstrated a response rate of 35%, with minimal morbidity.[48] Additional trials of lenalidomide are ongoing, but because it is available commercially, it should be considered in patients who have relapsed aggressive lymphoma and are not candidates for HD-ASCT.

Given these limited options, this group of patients should be referred for clinical trials. Numerous small molecule inhibitors (detailed below), antibodies, and other approaches with minimal toxicity are under study. The only way to definitively improve outcome and change the natural history for this large majority of patients with relapsed DLBCL is with the incorporation of novel agents and approaches.

Selected novel approaches under study for relapsed DLBCL: targeted agents from gene-expression analysis

Several datasets based upon gene-expression analysis of both DLBCL and the corresponding microenvironment have increased our understanding of resistance and our ability to predict which patients may be refractory to standard treatment. Even more exciting than enhanced prognosis, these analyses have revealed rational therapeutic targets. Several of these novel targeted agents are currently under study; a few examples are listed below.

Enzastaurin

Enzastaurin is a protein kinase c-beta inhibitor studied in DLBCL based upon gene-expression analysis demonstrating increased gene expression of protein kinase c-beta in fatal/refractory DLBCL. A phase 2 study of single-agent enzastaurin in relapsed DLBCL

demonstrated a subset of patients who responded and enjoyed prolonged PFS.[49] A randomized phase 3 trial comparing enzastaurin against placebo as a first remission maintenance treatment in high-risk DLBCL has been completed and is awaiting analysis.

BCR-signaling inhibitors

The BCR is present in DLBCL, and its engagement provides important survival signals. A subset of DLBCL appears to be particularly dependent upon this survival signal, even in the absence of antigen engagement (referred to as "tonic signaling").[50] Immediately downstream of the BCR is spleen tyrosine kinase (syk), which modulates and enhances the signal. Inhibition of syk has demonstrated activity against a subset of DLBCL in vitro,[51] and this has been confirmed in a clinical trial.[52] Additional rationale for this approach comes from the data that a subset of the poor-prognosis activated B-cell-like (ABC) lymphoma uses CARD11 for constitutive NF-κB pathway activity and survival.[53] Other targets downstream of syk in this pathway include Brutons tyrosine kinase and PI3K. Agents targeting these kinases are also under development in DLBCL.

NF-κB

Overexpression of NF-κB is a potential target in the ABC type of DLBCL, given constitutive activation of the NF-κB pathway in this subset. Bortezomib blocks degradation of phosphorylated inhibitor of NF-κB (IκBα), which inhibits NF-κB activity. To exploit this concept, Dunleavy et al treated patients with relapsed DLBCL with bortezomib alone, followed by a combination of bortezomib and doxorubicin-containing chemotherapy.[54] Single-agent bortezomib had no activity in DLBCL, but when combined with chemotherapy, it demonstrated a significantly higher response (83% vs 13%; $P < .001$) and median OS (10.8 vs 3.4 months; $P = .003$) in ABC compared with germinal center B-cell-like (GCB) DLBCL, respectively, as would be predicted from gene-expression profiling data. Combinations of bortezomib, and other proteasome inhibitors with histone deacetylase inhibitors appear to have particular promise in the laboratory, and currently are in phase I trials.[55] Novel inhibitors of NF-κB and IκBα are under development in this group of patients.

Immunomodulatory agents/microenvironment

As previously mentioned, lenalidomide has significant activity in relapsed DLBCL. Preliminary analysis suggest the benefit is largely limited to the ABC type of DLBCL.[56] Lenalidomide has pleotropic effects, including antiangiogenic effects, and effects on the immune microenvironment, suggesting a rationale for this agent particularly in "immune response-2" DLBCL.

Myc-positive and double-hit DLBCL

As mentioned, this subgroup appears to have the worst outcome. Frequently, concomitant bcl-2 translocations are present in this elderly patient population. Navitoclax is a targeted high-affinity small molecule that inhibits the anti-apoptotic activity of BCL-2 and BCL-XL, under study in a variety of lymphoma subtypes, including DLBCL.[57] c-Myc regulates the expression of Aurora A and B kinases, and these transcripts and protein levels are highly elevated in Myc-driven B-cell lymphomas in both mice and humans.[58] Studies of aurora kinase inhibitors are ongoing, both as single agents and in combination, with evidence of responses in aggressive lymphomas.

Bcl-6 inhibition

Both the ABC and GCB types of DLBCL appear to depend on bcl-6, even if a translocation is not present. Although still in preclinical evaluation, there is great promise to specific bcl-6 inhibitors that can kill cell lines and primary DLBCLs from human patients in vitro.[59]

Conclusions

Despite overall improvements in outcomes of DLBCL, relapsed/refractory disease remains a major cause of morbidity and mortality. For the subset of patients eligible, ASCT should be pursued with the recognition that results in the rituximab-treated population are inferior to historical results. Ongoing efforts are exploring novel conditioning regimens and maintenance approaches, but these will have limited impact on the whole population of relapsed/refractory DLBCL, because only a minority of patients proceed to this treatment. Patients not eligible for ASCT should be referred for clinical trials. Of particular interest are studies of rational agents derived from gene-expression analyses, which have low toxicity profiles and may ultimately contribute to changing the devastating natural history of relapsed/refractory DLBCL. Ultimately, these novel agents may be incorporated as part of first-line therapy, where the impact on preventing relapse will hopefully lead to significantly improved OS for patients with DLBCL.

Disclosures

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