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Treatment Strategies for Patients with Diffuse Large B-Cell Lymphoma: Past, Present, and Future

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Abstract

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

Keywords

Non-Hodgkin Lymphoma; Diffuse Large B-Cell Lymphoma; Lymphoma; chemoimmunotherapy; rituximab; treatment

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring form of non-Hodgkin lymphoma (NHL) in the Western world, encompassing about one-third of all lymphomas in adults. DLBCL is associated with an aggressive natural history, with a median survival of less than one year in untreated patients. The incidence of NHL increased dramatically from the 1970s until the mid 1990s with an estimated 66,360 new cases diagnosed in the United States in 2011.[1] The increase in incident cases of lymphoma and

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CONFLICT OF INTEREST DISCLOSURES

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DLBCL (~3–4% per year) occurred in both genders, across racial categories, and across age groups except the very young.[2–4] A number of factors may have contributed to the increased incidence including: more sensitive methods for diagnosing new cases, improvements in cancer reporting for hematological malignancies, changes in the classification systems used for of lymphoid malignancies, and the rise in human immunodeficiency virus (HIV) - associated DLBCL following the epidemic of HIV.[5] However, in sum these factors account for ~50% of the additional cases.[6] Other causes for the increase in DLBCL remain unknown.

The median age at diagnosis for DLBCL is in the seventh decade, although there do appear to be racial differences in the age of onset for DLBCL and other NHLs, with African Americans presenting at a younger age.[247] Patients with DLBCL commonly present with a rapidly enlarging painless, lymph node. However, in up to 40% of patients, the first site involved is extranodal. Approximately 15% of patients present with bone marrow involvement, about 1/3 have B-symptoms (fever, night sweats, and weight loss), nearly 1/2 have stage III/IV disease using the Ann Arbor staging system, and >1/2 have an elevated serum lactate dehydrogenase (LDH).[6] Patients diagnosed with DLBCL need to undergo full staging work-up which will help determine the treatment schedule but also help identify prognostic information and aid in predicting the expected likelihood of survival.

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

PATHOPHYSIOLOGY

As its name implies, DLBCL is a cancer of large B-cells that most commonly grows in a diffuse pattern completely effacing the normal lymph node architecture.[10] Given that DLBCL represents a clinically, biologically, and pathologically heterogeneous entity, the 2008 WHO classification system established several modifications to DLBCL classification to recognize multiple variants based on our improved understanding of the molecular and genetic abnormalities associated with DLBCL. [1112] Growing knowledge of the DLBCL biology has led to the understanding that DLBCL is actually mostly composed of two biologically distinct pathophysiologic entities, as initially described by Staudt and colleagues.[13] This group classified DLBCL by gene expression profiling into the Germinal Center B-cell subtype (GCB) and the activated B-cell (ABC) subtype, derived from different cells of origin. The Lymphoma/Leukemia Molecular Profiling Project reported approximately 60% GCB and 40% non-GCB in 240 newly diagnosed DLBCL patient biopsy samples examined by gene expression.[1415] Immunohistochemistry (IHC) assessment of CD10, BCL-6, MUM1 and other markers has been developed as a simpler counterpart to

gene expression profiling to classify cases of DLBCL into GCB and non-GCB (including ABC and other) subtypes using an assay that is more widely amenable to routine hematopathology practice.[16]

A series of Universities across the globe have employed the Hans algorithm to segregate subcategories of DLBCL. Alacacioglu et al. out of Turkey evaluated 50 patients and found 30% GCB and 70% non-GCB.[17] Saad et al. inspected blocks from a retrospective series of 30 patients and determined 57% were GCB and 43% non-GCB.[18] Fu et al. classified 131 patients from the Nebraska Lymphoma Study Group and determined 52% were GCB and 48% were non-GCB.[14] Four separate studies were conducted by prominent Japanese universities. Seki et al. out of Kurume, Japan, analyzed data from 730 patients and determined, by the Hans algorithm, that there were 48.2% GCB and 51.8% non-GCB.[19] Yamauchi et al., from Osaka, Japan, analyzed 81 young patients with DLBCL.[20] Using the Hans algorithm 31 were unclassified. Of the remaining 50 patients, 41% were GCB and 59% were non-GCB. Shiozawa et al. from Tokyo, Japan evaluated 248 patients out of which 29% had GCB and 71% had non-GCB DLBCL.[21] Thus, there appear to be racial and/or regional differences in the frequency of DLBCL subtypes.

While a consensus on the specific markers, techniques and algorithms to use for IHC to distinguish GCB versus non-GCB has not yet been reached; a positive predictive value of 73% to 87% for IHC compared to gene expression profiling has been reported based on CD10, BCL-6 and MUM1 IHC assays.[16] Meyer and colleagues recently examined published algorithms using IHC data to replicate microarray results.[22] The authors proposed implementation of the Tally algorithm as it was the most predictive of gene expression profiling while maintaining prognostic relevance and feasibility. The Tally algorithm scores two antigens of GCB (CD10 and GCET1) and two antigens of ABC (MUM1 and FoxP1) in no particular order and allots a score of 1 if expressed in more than 30% of cells. The immunophenotype with more positive antigens is determined. If the score is equal, the GCB antigen LMO2 serves as a tie breaker. In this study the Choi algorithm and the Hans algorithm had high concordance with the gene expression profiling results (87% and 86%, respectively), but the Tally method achieved 93% concordance and produced GCB and ABC subgroups that were significantly different in terms of event-free survival (EFS) and OS among DLBCL patients treated with rituximab-containing regimens.

TREATMENT

A. Limited stage disease

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

The SWOG 8736 trial, randomly assigned 401 patients to treatment with either 8 cycles of chemotherapy or three cycles of CHOP followed by 40 to 55 Gy of involved field radiation therapy (IFRT).[24] At a median follow-up of 4.4 years, the radiation arm had higher rates of 5 year PFS (77% *vs.* 64%) and OS (82% *vs.* 72%). However, data reported in abstract form, show that there were no longer differences in failure-free survival (FFS) and OS between the two treatment arms.[25] This was largely due to late relapses and lymphoma deaths after 5 years in patients who received abbreviated chemotherapy followed by radiation therapy. These findings suggest that three cycles of CHOP is inadequate systemic therapy, despite the fact that this trial included a relatively favorable group of patients. In this trial, half of the patients were younger than 60 years, two thirds of the patients had stage I disease, and patients with bulky stage II disease were excluded.

A similar study in patients with low risk stage I-II aggressive NHL (81% of patients had DLBCL), the GELA LNH 93–1 trial compared aggressive chemotherapy alone to abbreviated chemotherapy followed by radiation therapy. A total of 647 patients were randomized to three cycles of CHOP followed by IFRT or dose-intensified ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) followed by sequential consolidation without radiation therapy (RT).[26] Patients in this trial were younger than 61 years of age, had normal LDH levels and performance status, and two thirds had stage I disease. Although the addition of RT after three cycles of CHOP reduced relapses at initial sites of disease, it was not enough to overcome the excessive distant relapses after the abbreviated therapy. Patients randomly assigned to receive ACVBP, which had a theoretical dose-intensity of at least 150% of that delivered by three cycles of CHOP, had significantly higher 5-year event-free and OS rates. Although data on sites of relapse were not provided, one might surmise that most of the treatment failures on CHOP plus RT were at distant sites of disease outside the RT field. One conclusion of this trial might be that the micrometastatic tumor burden in patients with bulky-stage II disease is too high to be eradicated by 3 cycles of CHOP and seem better served receiving treatment designed for advanced disease. In another trial of ACVBP there were increases in secondary myelodysplasia/acute myelogenous leukemia and in lung cancer among men,[27] so this more aggressive regimen may not be ideal for young patients with limited stage disease.

In the ECOG 1484 trial, 172 patients with stage I or II, aggressive lymphoma in complete response (CR) after 8 cycles of CHOP were randomly assigned to receive 30Gy of IFRT or observation. Patients assigned to IFRT had a significantly higher rate of disease free survival (69% *vs.* 53%) and a trend toward better 5year OS (87% *vs.* 73%).[28] Elsewhere, the GELA LNH 93–4 trial reported on patients older than 60 years with localized aggressive lymphoma and normal LDH levels and performance status.[29] Two thirds of the patients had stage I disease and 8% had bulky disease. Patients were randomly assigned at diagnosis to four cycles of CHOP alone or four cycles of CHOP followed by RT to 40 Gy. Although the final number of patients was slightly lower than the target accrual, the recruitment of 574 patients gave this trial an 85% power to detect a 10% event free survival (EFS) difference. Patient and disease characteristics were well-balanced in the two arms and a central review of the technical details of the radiation therapy was conducted. At a median follow-up of 7 years, there were no significant differences in 5-year EFS (61% *vs.* 64% for chemotherapy alone and combined-modality therapy, respectively) and OS (72% *vs.* 68%) between the two arms.

There are no definitive randomized trials in the era of rituximab comparing chemoimmunotherapy to radiation therapy, there is however, a study comparing rituximab and CHOP followed by IFRT to historical controls.[30] In SWOG 0014, 60 patients with newly diagnosed aggressive, CD20-expressing NHL were treated with four doses of rituximab (infused on days -7, 1, 22, and 43) and CHOP (administered on days 3, 24, and 45), followed 3 weeks later by 40 to 46 Gy of IFRT. Patients had limited-stage disease and

at least one adverse risk factor as defined by the stage-modified IPI (nonbulky stage II disease, age>60 years, WHO performance status of 2, or elevated serum LDH). With the median follow-up of 5.3 years, treatment resulted in a PFS of 93% at 2 years and 88% at 4 years. OS was 95% at 2 years and 92% at 4 years. These results were compared with those from the historical group of patients treated without rituximab on SWOG 8736, demonstrating PFS of 78% and OS of 88% at 4 years. Taken together these trials demonstrate that abbreviated chemotherapy plus IFRT is at least as effective as a full course of the same chemotherapy regimen and may be associated with a lower rate of relapse at local sites of disease in the first years of follow-up. However, the later results of SWOG 8736 need to be considered before discarding the potential role for more cycles of therapy. In the future, imaging directed, response-adapted therapy may aid in determining which patients are likely to benefit most from radiation.[3132]

B. Advanced stage disease

For the majority of patients, DLBCL is a systemic disease at the time of diagnosis. At the completion of the initial staging evaluation, bulky stage II, stage III or stage IV disease is documented in approximately 75% of all DLBCL patients. Therefore, chemotherapy has been the critical component of treatment. Although the standard chemotherapy regimen has not significantly changed over the past three decades, the incorporation of monoclonal antibody therapy into the standard treatment program represents an improvement in OS for the majority of patients with DLBCL (Table 2). CHOP was known to cure approximately 30 percent of patients with advanced stages of intermediate-grade or high-grade NHL.[3334] However, studies at single indicated that more complex regimens such as low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD); prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM); and methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) could have higher short-term survival rates (55– 65%) but follow-up was limited and these new treatment programs were more difficult to administer, more toxic, and more costly.[35–37]

Therefore, in April 1986 a US Intergroup prospective, randomized phase III trial was initiated.[33] Each treatment group contained at least 218 patients. There were no significant differences among the groups in the rates of partial response (PR) and CR. At three years, 44% of all patients were alive without disease; there were no significant differences between the groups (41% in the CHOP and MACOP-B groups and 46% in the m-BACOD and ProMACE-CytaBOM groups; P = 0.35). OS at three years was 52% percent (50% in the ProMACE-CytaBOM and MACOP-B groups, 52% in the m-BACOD group, and 54% in the CHOP group; P = 0.90). Fatal toxic reactions were less common in patients treated with CHOP establishing this regimen as the standard of care for patients with DLBCL. This finding has been confirmed by other trials comparing more aggressive chemotherapy regimens to standard CHOP therapy.[38–40]

Nearly a decade later, rituximab was approved for follicular lymphoma and was soon applied to DLBCL. Rituximab is thought to induce lymphoma cell lysis through different immunologic or direct mechanisms, complement-mediated cytolysis, antibody-dependent cell cytotoxicity, and induction of apoptosis, and acts synergistically with chemotherapy[41–43] On the basis of phase 2 studies in which rituximab in combination with CHOP had a good safety profile and induced response rates in more than 90% of patients with indolent and aggressive lymphoma, the Groupe d'Etude des Lymphomas de l'Adulte (GELA) undertook a study to compare CHOP plus rituximab with CHOP alone in patients over the age of 60 years with DLBCL. The CR rate was significantly higher in patients receiving CHOP plus rituximab than in the group that received CHOP alone (76% *vs.* 63%,

P=0.0005). With a median follow-up of two years the OS was higher in the R-CHOP group.[44] Longer follow-up of this trial have demonstrated that EFS, PFS, and OS remained statistically significant in favor of the R-CHOP combination and actually continued to improve.[45]

In an attempt to improve on the results seen with CHOP-21 (administered every 21 days), trials have investigated the use of more dose intense chemotherapy. The most popular of these regimens is CHOP-14, which is given every 14 days with growth factor support. In a trial published by Economopoulos and colleagues, patients were treated with CEOP (cyclophosphamide, epirubicin, vincristine [Oncovin], and prednisone) every 2 weeks (CEOP-14) or every 3 weeks (the standard CEOP-21 regimen).[46] After 2002 rituximab was added to the regimen and therefore the trial examined the impact of adding rituximab to CEOP-14/CEOP-21 chemotherapy. The study reported similar response rates and survival between the two groups; however the addition of rituximab to both the 14 day and the 21 day regimens improved on OS and time to progression. Further study comparing dose intense chemotherapy to the standard with the addition of rituximab continue.

Cunningham et al. compared R-CHOP-14 to R-CHOP-21 in a phase III study of 1080 newly diagnosed DLBCL patients.[47] Patients were randomized to 8 cycles of standard R-CHOP-21 or 6 cycles of R-CHOP-14 with 2 additional cycles of single agent rituximab. All patients on R-CHOP-14 received G-CSF prophylaxis. There were more grade 3/4 neutropenia (77% *vs.* 37%) and febrile neutropenia (11% *vs.* 5%) in the R-CHOP-21 arm whereas there were more thrombocytopenia (5% *vs.* 9%) and anemia (1% *vs.* 3%) with R-CHOP-14. Grade 3/4 non-hematologic toxicity included infection (25% R-CHOP-21 *vs.* 19% R-CHOP-14), cardiac complications (< 1% R-CHOP-21 *vs.* 2.6% R-CHOP-14), and neurological issues (8% R-CHOP-21 *vs.* 11% R-CHOP-14). Overall response rates were similar between the 2 arms [63% CR or CRu (complete response underdetermined) on R-CHOP-21, and 58% on R-CHOP-14 (P = 0.15)]. With a median follow-up of 39 months, failure free survival (FFS) and OS (81% for R-CHOP-21 and 83% for R-CHOP-14) were identical. Subgroup analysis did not identify any subgroup that benefited from R-CHOP-14.

Delarue and colleagues presented the results of the planned interim analysis of the LNH03-6B, a multicenter, phase III open-label, randomized trial evaluating the efficacy of R-CHOP given every 14 days compared to R-CHOP given every 21 days.[48] 202 patients were randomized and 201 received study treatment (103 with R-CHOP-14 and 98 with R-CHOP-21). Median age was 72 years. Patients' characteristics were similar in both groups with a slightly higher proportion of patients with an age-adjusted international prognostic index (aaIPI) 2–3 in R-CHOP-14 arm (67% *vs.* 59%) whereas a higher proportion of patients in R-CHOP-21 arm presented with B symptoms (43% *vs.* 37%). 73 patients (71%) in R-CHOP-14 group and 74 patients (76%) in R-CHOP-21 group completed 8 cycles without progression. Overall response rates at 2 years including PFS (49% in RCHOP-14 *vs.* 63% in RCHOP-21) and OS (67% *vs.* 70%) were similar in both groups. Grade 3–4 hematological toxicity was more frequent in R-CHOP-14 group, with a higher proportion of patients receiving red cell or platelet transfusions and/or experiencing febrile neutropenia, resulting in higher proportion of patients hospitalized for adverse events. The results of this interim analysis of the LNH03-6B trial and other trials favor treatment with R-CHOP-21 in elderly patients with DLBCL, with trends toward higher efficacy and lower toxicity compared to R-CHOP-14.

Two trials conducted in the pre-rituximab era showed superiority of the intensive chemotherapy regimen ACVBP over standard CHOP in DLBCL [2649] In order to investigate the role of intensive chemotherapy associated with rituximab, the GELA initiated in 2003 a multicenter, phase III open-label, randomized trial comparing efficacy and safety of R-

ACVBP versus R-CHOP in younger DLBCL patients with an aaIPI of 1.[50] When compared with R-CHOP-21, R-ACVBP resulted in a similar CR rate (83% *vs.* 80%), and superior three-year EFS (81% *vs.* 67 %) and OS (92% *vs.* 84%) rates. R-ACVBP was associated with more hematologic and non-hematologic toxicity. Of importance, this regimen incorporates vindesine, an agent that is not broadly available in the US. Until larger randomized trials confirm a benefit from R-ACVBP, R-CHOP-21 remains the standard for most patients with DLBCL.

The role of high-dose therapy (HDT) and autologous stem cell therapy (ASCT) in the frontline treatment of patients with aggressive B-cell lymphoma has also been questioned, especially within the context of modern chemo-immunotherapy. In 2008, a meta-analysis included data from 15 randomized controlled trials with a total of 3,079 patients treated for aggressive NHL.[51] Overall, treatment-related mortality was 6% in the HDT group and not significantly different compared to conventional chemotherapy. Thirteen studies including 2,018 patients showed significantly higher CR rates in the group receiving HDT; however despite better CR rates, EFS and OS were the same whether patients were treated with conventional chemotherapy or high-dose chemotherapy followed by ASCT.

Also in question is whether patients with high-risk DLBCL may benefit from more intensive initial therapy involving HDT. To further define the role of HDT and ASCT, Glass et al. conducted a randomized phase III study comparing conventional therapy to HDT plus ASCT in young (18–60 years), high-risk (aaIPI 2 or 3) patients with aggressive B-cell lymphoma. [52] Patients received rituximab (375 mg/m^2 for 6 cycles) with 8 cycles of CHOEP-14 (CHOP + etoposide 300 mg/m^2, every 2 weeks) or 4 cycles of MegaCHOEP (cyclophosphamide,1500 mg/m^2 cycle 1, 4500 mg/m^2 cycles 2–3, 6000 mg/m^2 cycle 4; doxorubicin, 70 mg/m^2; vincristine, 2 mg; etoposide, 600 mg/m^2 cycle 1, 960 mg/m^2 cycles 2–3, 1480 mg/m^2 cycle 4; prednisone, 500 mg) every 21 days followed by ASCT. The CR/CRu rate was similar between the 2 arms (79% R-CHOEP-14 *vs.* 71% R-Mega-CHOEP, P = not significant [NS]). Three-year EFS (69.5% R-CHOEP-14 *vs.* 61.4% R-MegaCHOEP, P = 0.140), PFS (74% R-CHOEP-14 *vs.* 70% R-MegaCHOEP), and OS (85% R-CHOEP-14 *vs.* 77% R-MegaCHOEP, P = 0.081) were also similar between the 2 arms.

Adverse events (AE) were more common with R-MegaCHOEP. Only 57.5% of patients on the R-MegaCHOEP arm completed all cycles of therapy compared to 88% of patients on the R-CHOEP-14 arm. Grade 3/4 AE were higher with R-MegaCHOEP. In summary, first-line treatment with HDT and rituximab (R-MegaCHOEP) was not superior to conventional treatment (R-CHOEP-14) in young, high-risk patients. Furthermore, toxicity was increased with the intensified regimen. This SWOG led intergroup trial investigated the benefit of autologous transplant in first remission patients with bulky stage II, III, and IV disease, high-intermediate/high IPI score, diffuse NHL after 5 cycles of CHOP±R.[53] Primary endpoints were toxicity and 2 year PFS and OS for randomized patients; the study was powered to detect a hazard ratio of 1.50 between arms. Registered patients were treated with CHOP or R-CHOP for 5 cycles. Patients who achieved a PR or better were randomized to 1 additional cycle of CHOP/R-CHOP followed by ASCT or 3 additional cycles of CHOP/R-CHOP. Initial results, demonstrated that the addition of ASCT resulted in a significantly higher rate of PFS at two years (69% *vs.* 56%) but no difference in OS (74% *vs.* 71%).

C. Relapsed/Refractory

Despite our understanding of the heterogeneity of DLBCL and an increasing number of treatment combinations and experimental agents, most clinicians continue to treat DLBCL with single management strategy at initial presentation and at relapse. Novel approaches to managing patients with relapsed DLBCL are needed.[3254] The question of how best to manage relapsed patients was addressed by a multicenter trial known as the PARMA trial

comparing ASCT to conventional salvage therapy. In this trial, 215 patients in first or second relapse were given two cycles of intensive combination chemotherapy. The 109 patients who responded were randomly assigned to receive four more cycles of chemotherapy or ASCT. With a 5 year median follow-up, EFS and OS were significantly improved with transplantation (46% *vs.* 12% and 53% *vs.* 32% respectively).[55] A number of standard regimens exist for salvage lymphoma therapy including ICE (ifosphamide, carboplatin, etoposide), ESHAP (etoposide, methyl prednisolone, high dose cytarabine, cisplatin), DHAP (dexamethasone, cisplatin, cytarabine), and GDP (dexamethasone, cisplatin, gemcitabine) with varying response rates.

The choice of salvage therapy is still debated although it is clear that the addition of rituximab to the re-induction regimen yields superior results compared to the same regimen without rituximab. For example, the HOVON group randomized relapsed patients to DHAP with or without rituximab. Following two cycles, 75% of the patients in the R-DHAP arm had responsive disease versus 54% in the DHAP arm (P=.01).[56] With a median follow-up of 24 months, there was a significant differences in PFS (52% *vs.* 31% P=<.002) and OS in favor of the R-DHAP arm. Moreover, rituximab does not appear to impair stem cell engraftment or adversely affect transplantation toxicity, and is associated with improved PFS when given prior to ASCT for DLBCL.[57] In another study validating the use of rituximab at relapse, Kewalramani and colleagues conducted a retrospective review of patients treated with R-ICE and compared them to historical controls treated with ICE alone.[58] R-ICE given for three cycles produced CR in 53%, and no patient had R-ICE related toxicity that precluded ASCT. It is important to note that patients in both the HOVON and Kewalramani studies had received prior induction therapy without the addition of rituximab, whereas the studies below provide data on DLBCL patients' response to salvage therapy when they had previously received rituximab with first-line therapy.

The choice of salvage chemotherapy after R-CHOP failures was addressed by a prospective multicenter phase III study, the COllaborative trial in Relapsed Aggressive Lymphoma (CORAL).[59] DLBCL patients in first relapse or who were refractory after first-line therapy were randomly assigned to salvage therapy with R-ICE or R-DHAP. After three courses of therapy, responders were treated with HDT and ASCT. The response rates for R-ICE and R-DHAP were identical, suggesting that either regimen can be used for salvage therapy. However, an analysis of the 396 patients enrolled on the trial also showed much poorer outcomes for patients who had: 1) second line IPI score of 2/3 vs. 0/1 (3-year EFS 18% *vs.* 40%, respectively), 2) relapse < 12 months after completion of first-line therapy (20% *vs.* 45%, respectively) or 3) prior rituximab exposure in the front line setting (21% *vs.* 47%, respectively), regardless of their type of salvage therapy. Moreover, patients who relapsed early following upfront R-chemotherapy had a very poor prognosis with a 3-year PFS of 23%, which remained poor even when consolidated with HDT and ASCT (3-year PFS of 39%).[59] A second randomization in this trial included 242 evaluable patients randomized to observation or rituximab maintenance. There was no difference in EFS (median EFS: 58.2 months with observation *vs.* 57.6 months with rituximab, P = 0.7435), PFS (median PFS: 58.2 months with observation *vs.* 57.6 months with rituximab, P = 0.8314), or OS (median OS: 62.9 months with observation *vs.* not reached with rituximab, P = 0.7547) regardless of the induction regimen used. There also was no difference in PFS or OS between patients achieving a CR/CRu compared to PR. This trial highlights that rituximab maintenance does not improve EFS, PFS, and OS after ASCT following first relapse, and other data suggest that maintenance rituximab has no defined role for patients with DLBCL.[60]

CONCLUSIONS

DLBCL remains the most commonly occurring lymphoma in the Western world. This disease is uniformly fatal without treatment, but the majority of patients are cured with standard R-CHOP chemoimmunotherapy. Debate remains regarding the role of radiation for patients with limited stage disease, but R-CHOP-21 for 6–8 cycles has clearly emerged as the standard of care for patients with advanced stage disease. Emerging data on immunohistochemically defined subsets of DLBCL may help us to risk stratify patients and define subtype-specific therapies in the future. While autologous stem cell transplant can salvage and cure patients with relapsed DLBCL, questions are emerging regard the benefits of this approach for patients who relapse early after R-CHOP. Given that we now cure more patients upfront, those who relapse early may be a poorer risk population for whom novel treatment approaches are needed.

FUTURE DIRECTIONS: NOVEL AGENTS

At present there is no standard therapy in the third-line setting or for patients with poor risk biological subtypes of DLBCL. For such patients, disease progression has been managed with a wide range of treatments, including multi-agent regimens, single agents or with a variety of new experimental drugs.[61] Recently, there has been a shift from identifying classical cytotoxic agents to molecules that target specific pathways involved in signal transduction, apoptosis, and differentiation. The improved understanding of DLBCL subtypes and gene-expression profiles, has led to subsequent development of targeted drugs and regimens for DLBCL which may help address this clinical problem. Several novel agents are undergoing evaluation in DLBCL, both as single agents in the relapsed setting and in combination with R-CHOP. Some examples include other antibody therapies, lenalidomide, SGN-40, Syk inhibitors, enzastaurin, histone deacetylase inhibitors, bortezomib, anti-survivin agents, bevacizumab, and mTOR inhibitors (Table 3).

Lenalidomide, an approved agent that is used in myelodysplastic syndrome and myeloma has been studied in patients with relapsed aggressive lymphomas. There have been phase II trials conducted with this agent in relapsed or refractory aggressive NHL. In the first study 49 patients received lenalidomide (25mg/day) administered on days 1–21, every 28 days for 52 weeks as tolerated or until disease progression.[62] The median age was 65 years. The most common histology was DLBCL (53%). The overall response rate (ORR) was 35% for all patients, 19% for DLBCL patients and 53% in mantle cell lymphoma (MCL). The estimated median duration of response was 6.2 months (range, 0 to 12.8 months), and median PFS was 4.0 months (range, 0 to 14.5 months). Based on the promising results of this study, an international phase II trial was conducted in 217 patients.[63] In patients with DLBCL (n=108) the ORR was 28% and PFS of 2.3 months. Three patients (4%) achieved CR and 18 patients (25%) had a PR. Eleven patients (15%) had stable disease. The drug was tolerated well and the toxicity profile was similar in both trials. The clinical data available so far suggest that lenalidomide represents a promising drug for lymphoma therapy.Lenalidomide also is currently being investigated in combination with R-CHOP[64] and as maintenance therapy for patients with DLBCL.

Bortezomib, a proteasome inhibitor that demonstrated single-agent activity leading to its approval for use in relapsed MCL,[65] is another agent hypothesized to have activity in DLBCL based on molecular profiling. ABC and primary mediastinal DLBCL subtypes are known to have high levels of activity in the NF-kB pathway, which is targeted by bortezomib. Furman et al. completed a phase I/II study of bortezomib-R-CHOP in patients with previously untreated DLBCL or MCL.[66] Based on the phase I results, bortezomib, at 1.3 mg/m^2 on days 1 and 4 with the standard R-CHOP regimen given in a 21-day cycle, was

recommended for further study and 76 additional patients, including 40 patients with DLBCL, were enrolled in the phase 2 portion of the study. Of 35 response-evaluable DLBCL patients, the ORR was 100%, and 90% of patients had a CR (17 patients) or an unconfirmed CR (11 patients). Thirty-one of these evaluable patients had tumor subtyped as GCB or non-GCB using the Hans method. The 2-year PFS (~70%) and 2-year OS (~85%) in the 17 patients with the non-GCB subtype were similar to that in the 14 patients with the GCB subtype, suggesting that the addition of bortezomib to R-CHOP improved the outcome of this poor prognosis group.

A European-based phase II study randomized 49 newly diagnosed B-cell lymphoma patients to 4 bortezomib schedules in combination with R-CHOP.[67] Across these schedules an 88% CR/CRu rate was reported for 16 patients with aggressive lymphoma (DLBCL and transformed follicular lymphoma). Dunleavy et al. conducted a phase I/II study of bortezomib with dose-adjusted administration of etoposide, vincristine, and doxorubicin for 96 hours with bolus doses of cyclophosphamide and oral prednisone (EPOCH) in patients with relapsed aggressive lymphoma.[68] This study enrolled 33 DLBCL patients and the ORR was ~40%. However, 27 patients had GCB/non-GCB subtyping performed which indicated that the typically poor outcome, non-GCB subtype was particularly sensitive to this combination. The ORR favored non-GCB over GCB (83% *vs.* 13% [P=0.0004), as did the CR rate (42% *vs.* 7%). There was also a significant difference in OS favoring the non-GCB subtype (P=0.0026). The results of this study are the opposite of what would be expected, with the poor prognosis (non-GCB) group achieving superior outcomes.

In the phase 1/2 trial described above, patients with non-GCB DLBCL had similar PFS and OS to GCB patients when bortezomib was added to RCHOP,[69] suggesting that bortezomib may help to overcome the adverse outcomes associated with the ABC subtype. A multicenter, clinical trial that uses the Hans method to subtype DLBCL patients and then randomizes non-GCB patients to bortezomib plus R-CHOP or R-CHOP is now underway.

Enzastaurin (LY317615.HCl), an acyclic bisindolyl maleimide, is a potent small-molecule inhibitor of serine/threonine kinases. It inhibits kinase activity by competing with ATP for the enzyme's ATP-binding site. It was initially developed as a selective inhibitor of PKCβ, with a 50% inhibitory concentration (IC50) of 6 nmol/l. Enzastaurin also inhibits other PKC isoforms at higher concentrations. Robertson et al. reported the first multicenter phase II study of enzastaurin in patients with relapsed or refractory DLBCL.[70] Enzastaurin was given orally once daily until disease progression or unacceptable toxicity occurred. Study end-points included freedom from progression for two or more 28-day cycles, objective response, and toxicity. Treatment with enzastaurin was well tolerated. A small subset of patients showed benefit from the treatment. After the success of this drug in phase II trials, phase III studies being conducted include: daily enzastaurin vs. placebo in prevention of relapse in DLBCL, combination trials of enzastaurin with rituximab, gemcitabine and oxaliplatin (R-GEMOX) in patients with DLBCL new or relapsed setting.

Another target identified through gene expression profiling, B-cell receptor (BCR)-mediated survival signals, can be blocked by an inhibitor of spleen tyrosine kinase (Syk), fostamatinib disodium, which induces apoptosis in B-cell lymphoma cell lines and primary tumors. Fostamatinib disodium, the first clinically available oral Syk inhibitor, was recently tested in patients with recurrent B-cell NHL. Dose-limiting toxicity in the phase I portion was neutropenia, diarrhea and thrombocytopenia and 200 mg bid was chosen for Phase II testing. Sixty-eight patients with recurrent B-NHL were then enrolled in 3 cohorts: DLBCL; FL, and other NHL, including MCL; marginal zone/MALT; lymphoplasmacytic; and SLL/CLL. Common toxicities included diarrhea, fatigue, cytopenias, hypertension and nausea.

Objective response rates were 22% for DLBCL, 10% for FL, 55% for SLL/CLL and 11% for MCL. Median PFS was 4.2 months, and median response duration exceeded 4 months.[71]

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

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Table 1

Summary of Clinical trials for the treatment of Localized DLBCL

Trial Sample Size	Regimen (s)	Overall Response Rate	Survival Comparison	Reference
SWOG 8736 (n=401)	CHOP×3 + IF-XRT vs CHOP×8	ORR 75% vs 73%	EFS 76% vs 67% (p=0.003) OS 82% vs 74% (p=0.02)	24, 25
GELA LNH 93–1 (n=647)	ACVBP×6 vs CHOP×3 + IF-XRT	ORR 95% vs 93%	EFS 82% vs 74% (p<0.001) OS 90% vs 81% (p=0.001)	26
ECOG 1484 (n=353)	CHOP×8 + IF-XRT vs CHOP×8	Not reported	EFS 69% vs 53% OS 87% vs 73	28
GELA LNH 93–4 (n=576)	CHOP×4+IF-XRT vs CHOP×4	ORR 91% vs 92%	EFS, 61% *vs.* 64% OS 72% *v* 68%	29
SWOG 0014 (n=60)	R-CHOP×3 + IF-XRT vs Historical controls	Not recorded	EFS 88% vs 78% OS 92% vs 88%	30

Table 2

Summary of Key Clinical trials for the treatment of Advanced stage DLBCL

Trial Sample Size	Regimen (s)	Overall Response Rate	Survival Comparison	Reference
SWOG/ECOG (n=899)	CHOP vs MACOP-B vs m-BACOD vs ProMACE-CytaBOM groups	80 % CHOP ;82% m-BACOD; 83% MACOP-B and 87% ProMACE-CytaBOM	3-year OS 50% ProMACE-CytaBOM and the MACOP-B groups, 52% m-BACOD group, 54%CHOP	33
GELA LNH 98.5 (n-399)	RCHOP vs CHOP	CR/CRu - 76% vs 65%	5-year OS 58% R-CHOP vs. 45% CHOP	44, 45
ECOG 4494 (n=632) Responders (n=415)	RCHOP vs CHOP Responders: Maintenance R vs. observation	ORR 77% vs 76%	3-year FFS 53% R-CHOP and 46% CHOP 3-year OS 67% R-CHOP and 58% CHOP	Habermann 2006
MInT (n=823)	RCHOP vs CHOP	CR/Cru - 86% *vs* 68%	OS 93% for RCHOP vs 84% for CHOP	Pfreundschuh
Cunningham (n=1080)	RCHOP 21×8 vs RCHOP 14×8	ORR 88% vs 99%	OS at 2 years was 81% for R-CHOP21 and 83% for R-CHOP14 arm.	47
GELA LNH 03-6B (n=202)	RCHOP 21×8 vs RCHOP 14×8	OR 84%for RCHOP 21 vs 81% for RCHOP 14	OS at 2 year was 70% for RCHOP21 and 67% for RCHOP14	48
GELA LNH03-2B (n=380)	R-ACVBP vs R-CHOP	ORR was 90.3% in the R-ACVBP group and 88.5% in the R-CHOP group (p=0.57).	OS at 3 years was 92.2% for R-ACVBP *vs* 83.8%	50

Table 3

Novel Agents currently in clinical trials for Diffuse Large B Cell Lymphoma

Mechanism of Action	Drug(s)
Antibodies against VEGF	Bevacizumab
PKC-β inhibitor	Enzastaurin
Anti-CD22	Epratuzumab,
mTOR inhibitor	Everolimus, Temsirolimus
Immunomodulatory agents	Lenalidomide
Syk-kinase inhibitor	Fostamatinib
NEDD8 activating enzyme inhibitor	MLN4924
Proteasone Inhibitor	Bortezomib, Carfilzomib
Histone Deacetylase Inhibitor	Panobinostat, MGCD013