Treatment of Aggressive Non-Hodgkin’s Lymphoma: A North American Perspective

By Laurie H. Sehn, MD, MPH [4] and Joseph M. Connors, MD [5]

The most common subtype of aggressive non-Hodgkin's lymphoma is diffuse large B-cell lymphoma (DLBCL). Diffuse large B-cell lymphoma represents a heterogeneous entity, with 5-year overall survival rates ranging from 26% to 73%. Microarray gene expression studies have confirmed that biologically distinct subgroups exist within DLBCL, and can be correlated with outcome. Initial management is usually guided by stage of disease at presentation. Approximately 25% of patients with DLBCL present with limited-stage disease and are treated with combined-modality therapy (brief chemotherapy and involved-field radiation). Most patients present with advanced-stage disease and require treatment with an extended course of chemotherapy. The CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) chemotherapy regimen has been the mainstay of therapy since its development in the 1970s, as more intensive chemotherapy regimens failed to show additional benefit. The era of monoclonal antibodies has transformed treatment practices for aggressive lymphoma and has led to a significant improvement in outcome. A randomized trial comparing the use of rituximab (Rituxan), a chimeric anti-CD20 IgG1 monoclonal antibody, combined with CHOP chemotherapy vs CHOP chemotherapy alone for elderly patients with advanced-stage DLBCL demonstrated a significant benefit for the combination approach. This finding has now been confirmed in two additional randomized, controlled trials and a population-based analysis, making CHOP and rituximab the standard of care for all newly diagnosed patients with DLBCL. Despite this advance, newer therapies are needed and many are under active investigation. The insights gained from molecular techniques such as gene expression profiling should permit identification of additional lymphoma-specific therapeutic targets and the development of novel agents that take into account underlying biology and allow for greater tailoring of therapy.

The World Health Organization (WHO) classification of non-Hodgkin's lymphoma (NHL) recognizes more than 30 different subtypes of NHL.[1] The term aggressive NHL refers to those subtypes that grow rapidly (proliferation index > 40%) and would often be fatal within months without appropriate therapy. The most common subtype of aggressive NHL is diffuse large B-cell lymphoma (DLBCL), which will be the main focus of this review. Diffuse large B-cell lymphoma accounts for approximately 30% to 40% of all newly diagnosed cases of NHL and more than 80% of aggressive lymphomas.[1] Prognosis Diffuse large B-cell lymphoma represents a heterogeneous entity. Multiple morphologic variants are recognized within the WHO classification, and patients exhibit a wide range of clinical presentations. The International Prognostic Index (IPI) remains the primary clinical tool used for predicting outcome for aggressive NHL.[2] Based on the number of negative prognostic features present at the time of diagnosis (age > 60 years, stage III/IV disease, elevated lactatedehydrogenase [LDH] level, Eastern Cooperative Oncology Group [ECOG] performance status ≥ 2, more than one extranodal site of disease), the 5-year overall survival rate rangesfrom 26% to 73%.[2] Only about half of all presenting patients will be cured of their lymphoma. The clinical factors conferring poor prognosis are likely surrogate vari-ables for intrinsic molecular heterogeneity. Multiple molecular markers, such as overexpression of bcl-2 and bcl-6, have been shown to be predictive of outcome in DLBCL.[3] More recently, microarray gene expression studies have confirmed that biologically distinct subgroups exist within DLBCL, and can be correlated with outcome.[4-7] Alizadeh and colleagues demonstrated that at least two major subtypes can be recognized based on the pattern of gene expression: one with a gene expression profile similar to normal germinal center B cells (GCB), and the other mimicking activated peripheral blood B cells (ABC).[4,5] Patients with the GCB profile have a significantly better overall survival, and the gene expression pattern provided additional prognostic information independent of the IPI. Several investigators have used the information provided through gene array studies to develop more clinically applicable models for subclassifying patients according to genetic heterogeneity. Using simple immunohistochemistry techniques and tissue arrays, Hans and colleagues demonstrated that patients could be categorized into GCB and non-GCB subtypes based on the expression of six
genes.[8] In a separate study, Lossos and colleagues used polymerase chain reaction (PCR) technology to develop a prediction model based on the six genes with highest predictive capacity as identified in gene array studies.[9] Efforts are currently under way to develop updated prognostic models that will combine both relevant clinical and molecular factors to further refine outcome prediction. This greater insight into the underlying biology of DLBCL may allow for the development of newer targeted therapeutic agents and tailored therapy options. However, it is not currently known how this information should be used to influence treatment decisions. **Initial Treatment of Limited-Stage Disease** Approximately 25% of patients with DLBCL present with limited-stage disease (stage I and non-bulky stage II). These patients have a variable outcome depending on the number of negative features present at diagnosis, with a 5-year overall survival ranging from 50% to 95%.[10,11] Using a stage-modified version of the IPI (including four factors: age > 60 years, elevated LDH, ECOG performance status ≥ 2, stage II disease), a very favorable subgroup can be identified (stage I with no risk factors) with a 5-year overall survival of greater than 90%, with remaining patients having a 5-year overall survival of approximately 70%.[12] The presence of bulky stage II disease (≥ 10 cm) has been associated with a poorer prognosis; therefore, in North America these patients are treated similarly to those with advanced-stage lymphoma.[13] Historically, patients with limited-stage disease treated with radiation therapy alone frequently relapsed at distant sites.[14] Chemotherapy was introduced in an attempt to eradicate micrometastases and improve outcomes. The rationale for a combined-modality approach using a brief course of chemotherapy followed by involved-field radiation therapy included maximizing local and systemic control and minimizing toxicity.[15] With a median follow-up of 4.4 years, a large randomized trial performed by the Southwest Oncology Group (SWOG) compared combined-modality treatment-consisting of three cycles of CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], and prednisone) plus radiotherapy-with chemotherapy alone (eight cycles of CHOP). Investigators saw improved progression-free survival, overall survival, and lesser toxicity with the combined-modality approach.[11] This trial was later updated with a median follow-up of 8.2 years.[12] Kaplan-Meier estimates showed overlapping curves at 7 years for failure-free survival and at 9 years for overall survival, due to an increased number of delayed relapses and deaths from lymphoma in the combined-modality group. Given its short duration, lower toxicity, and the early advantage seen in the first 7 to 9 years, combined-modality therapy (brief chemotherapy and involved-field radiation) has remained the standard of care at many centers. Recently, Horning and colleagues updated results of a randomized trial comparing involved-field radiotherapy (30 Gy) vs no further treatment for limited-stage patients with aggressive diffuse lymphoma who achieved a complete remission (CR) following extended course chemotherapy (eight cycles of CHOP).[16] Patients who achieved a partial remission (PR) were all treated with radiotherapy (40 Gy) in an attempt to induce a CR. Of note, this trial included patients with bulky stage II disease. Among 172 patients who achieved a CR following CHOP, the 6-year disease-free survival was improved in the radiotherapy group (73% vs 56%, \( P = .05 \)), but no difference in overall survival was seen. For patients who achieved a PR and received radiotherapy, there seemed to be no advantage obtained from conversion to CR. In this trial, extending the therapy to eight cycles of CHOP and radiotherapy had no advantage over eight cycles of CHOP alone, and thus it may be inferred that eight cycles of CHOP and radiotherapy offers no advantage over three cycles of CHOP and radiotherapy. Several recent trials have reported results in favor of chemotherapy alone for patients with limited-stage aggressive lymphoma. The Groupe d’Etude des Lymphomes de l’Adulte (GELA) has reported results of a trial comparing the ACVBP regimen (an intensive schedule of doxorubicin [Adrmycin], cyclophosphamide, vindesine, bleomycin, and prednisone, followed by consolidation with methotrexate, ifosfamide, etoposide, and cytarabine) vs three cycles of CHOP and involved-field radiotherapy.[17] This trial demonstrated a significant benefit for ACVBP in both 5-year event-free survival and overall survival. However, not only was ACVBP associated with significant toxicity, but this trial included patients with bulky stage II disease, a group that has been shown to do poorly with three cycles of CHOP and radiotherapy and should be treated the same as patients with advanced-stage lymphoma. A second trial reported by GELA compared four cycles of CHOP to four cycles of CHOP and involved-field radiotherapy, for elderly patients (> 60 years) with limited-stage aggressive NHL and no adverse risk factors according to the age-adjusted IPI.[18] In this trial, the addition of radiotherapy offered no advantage in terms of event-free or overall survival, and in the subgroup of patients who were older than 69 years, there was a survival advantage for chemotherapy alone. Although intriguing, this trial has only been presented in abstract form and further interpretation must await final publication. **Initial Treatment of Advanced-Stage Disease** Most patients with DLBCL present with advanced-stage disease at diagnosis. The CHOP chemotherapy regimen has been the mainstay of therapy since its
Treatment of Aggressive Non-Hodgkin’s Lymphoma: A North American Perspective

Published on Cancer Network (http://www.cancernetwork.com)

...development in the 1970s.[19] Early attempts to improve outcomes through the creation of more intensive chemotherapy regimens by adding in non-cross-resistant drugs failed to show additional benefit. An American Intergroup trial randomized patients to one of three intensive chemotherapy regimens (MACOP-B, m-BACOD, ProMACE-CytaBOM)* or standard CHOP.[20] This trial demonstrated that CHOP chemotherapy was as effective as the more intensive chemotherapy regimens, achieving a 3-year disease-free survival rate of 54%, with lesser toxicity. Thus, CHOP has remained the standard of care. Continued attempts to improve upon CHOP chemotherapy have focused on a variety of alternative chemotherapy strategies, including increased dose intensity (additional cytotoxic agents or higher doses) and increased dose density (interval reduction in drug delivery).

The NHLB1 and NHL-B2 trials from Germany explored these strategies by randomizing patients to one of four different chemotherapy regimens: standard CHOP (CHOP-21), CHOP administered at 2-weekly intervals with granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) support (CHOP-14), or these same regimens with the addition of etoposide (CHOEP-14 or CHOEP-21).[21,22] The NHL-B1 trial included 710 young patients (ages 18-60 years) with good prognosis (normal LDH) aggressive NHL.[22] The trial was analyzed according to the 2*2 factorial protocol design, comparing the two CHOP cohorts with the two CHOEP cohorts, and the two biweekly regimens with the two 3-week regimens independently. With a median observation time of 58 months, the addition of etoposide resulted in an improved 5-year event-free survival (69.2% vs 57.6%, \( P = .0004 \)), but no difference in overall survival. The reduction to biweekly intervals did not significantly improve event-free survival in this young patient cohort, but did improve overall survival (\( P = .05 \)). In NHL-B2, 689 elderly patients (ages 61-75 years) with newly diagnosed aggressive NHL were enrolled and eligible for evaluation.[21] CHOP-14 resulted in a significant improvement in 5-year event-free survival (43.8% vs 32.5%) and 5-year overall survival (53.3% vs 40.6%) compared with standard CHOP-21. However, the addition of etoposide in this elderly subgroup caused a substantial increase in toxicity and offered no advantage in outcome. Examined together, these trials offer somewhat paradoxical results in these two different patient subgroups, making firm conclusions regarding the benefit of either approach difficult. The GELA compared the intensive conventional chemotherapy regimen ACVBP with standard CHOP in previously untreated patients with poor-risk aggressive NHL.[23] A total of 635 elderly patients (ages 61-69 years) with at least one negative prognostic factor according to the age-adjusted IPI were eligible for evaluation. Both the 5-year event-free survival (39% vs 29%, \( P = .005 \)) and the 5-year overall survival (46% vs 38%, \( P = .036 \)) were significantly higher for patients treated with ACVBP. However, treatment-related deaths were higher in the ACVBP group (13% vs 7%, \( P = .014 \)). In addition, an evaluation of patients treated on multiple trials of ACVBP demonstrated an increase in secondary myelodysplastic syndrome and acute leukemias, and an increase in lung cancer in men.[24] Investigators at the National Cancer Institute in the United States have explored dose-adjusted EPOCH, an approach that combines infusional therapy with dose escalation to patient tolerance.[25] This protocol involves the administration of etoposide, vincristine, and doxorubicin for 96 hours, with bolus doses of cyclophosphamide and prednisone. The doses of etoposide, doxorubicin, and cyclophosphamide were adjusted by 20% in each subsequent course to achieve a nadir neutrophil count of 0.5 \( \times \) 10^9/L. Fifty previously untreated patients with large B-cell lymphomas were entered into a multi-institutional phase II trial. Median age was 48 (range: 20-88 years), and 44% had a high/intermediate- or high-risk IPI score. There was a high response rate (92% CR) and with a median follow-up time of 62 months, progression-free survival and overall survival were 70% and 73%, respectively. Investigators were able to escalate the doses in 58% of cycles. Initial use of high-dose therapy (HDT) and autologous stem cell transplantation has been investigated in aggressive NHL and remains controversial. Multiple studies have been reported, with conflicting results.[26] While several studies have suggested a benefit for up-front autologous transplant for patients with poor-risk disease, others have been negative.[27,28] Recently, Milpied et al presented results of a randomized trial comparing HDT to standard CHOP in young patients (15-60 years) with untreated aggressive NHL with low-, low/intermediate-, or high/intermediate-risk disease according to the age-adjusted IPI.[29] A total of 197 patients were randomized; median follow-up was 4 years. The 5-year event-free survival was significantly improved in the HDT group (55% vs 37%, \( P = .037 \)), but the 5-year overall survival did not meet statistical significance (71% vs 56%, \( P = .076 \)). On subset analysis, only patients in the high-intermediate risk group seemed to benefit, with both an improvement in event-free and overall survival. This trial suggests some patients may benefit from HDT; however, many patients treated with HDT would likely have been cured with CHOP alone and were exposed to unnecessary toxicity. As HDT has been shown to cure a subset of patients with relapsed disease, it is likely that some patients may benefit from this treatment earlier in their course. The challenge remains trying to identify the appropriate...
subset that may benefit. An ongoing randomized trial being led by SWOG may further clarify the role of HDT in this setting.

Thus far, none of these newer approaches have replaced CHOP as standard front-line therapy for aggressive NHL. Many trials have been performed in selected subgroups of patients, making generalizability difficult. In addition, the toxicity profiles have been substantially increased compared with CHOP. Most importantly, all of these trials have been performed prior to the availability of targeted therapy with monoclonal antibodies. Whether increasing dose intensity or dose density will offer an advantage when used in conjunction with a monoclonal antibody remains to be determined. Ongoing trials will help to answer these questions.

Addition of Rituximab to Chemotherapy

The era of monoclonal antibodies has transformed treatment practices for aggressive lymphoma and has led to a significant improvement in outcome. Rituximab (Rituxan), a chimeric anti-CD20 IgG1 monoclonal antibody, was approved by the US Food and Drug Administration (FDA) in 1997 for treatment of relapsed and refractory follicular lymphoma.[30] Rituximab targets the CD20 cell surface protein present on mature B cells and most B-cell malignancies. Its effects are likely multifactorial and include complement-dependent cell lysis, cell-mediated cytotoxicity, and induction of apoptosis.[31] Preclinical models suggested a synergistic effect when rituximab was combined with chemotherapy and early clinical trials demonstrated a minimal increase in toxicity.[32] Early studies also indicated activity in DLBCL, with a single-agent response rate of 37%.[33] The feasibility and safety of combining CHOP with rituximab was demonstrated in a phase II trial that reported a higher than expected CR rate of 61%.[34] The GELA Trial

The GELA performed the first randomized, controlled trial demonstrating the benefit of adding rituximab to chemotherapy for the treatment of DLBCL.[35] This trial compared eight cycles of CHOP chemotherapy to eight cycles of rituximab and CHOP (R-CHOP) in elderly patients (age ≥ 60 years) with newly diagnosed advanced stage DLBCL. Rituximab was administered at 375 mg/m² on day 1 with each cycle of CHOP. A total of 399 patients were included in this trial: 197 in the CHOP arm and 202 in the R-CHOP arm. Patients in the R-CHOP arm had a higher response rate (CR/unconfirmed CR rate 75% vs 63%, \( P = .005 \)) and a lower rate of progression on treatment (9% vs 22%), resulting in both a significantly improved event-free and overall survival. These results have been recently updated with a median follow-up time of 5 years.[36] The benefit seen with the addition of rituximab has been maintained over time, indicating an improvement in the cure rate for this patient population (5-year event-free survival 47% vs 29%, \( P = .00002 \); 5-year overall survival 58% vs 45%, \( P = .0073 \)) (Figure 1). The addition of rituximab did not result in any increase in clinically relevant toxicity. Subgroup analyses of the GELA trial have demonstrated several interesting observations. Patients were stratified according to age-adjusted IPI, and both the low- and high-risk patients were shown to benefit from the addition of rituximab. However, patients in the low risk group seemed to experience the greatest degree of benefit.
Outcome was also analyzed according to the level of bcl-2 protein expression.[37] The impact of the addition of rituximab to CHOP was largely seen in patients who overexpressed bcl-2, suggesting that rituximab could overcome the chemotherapy resistance seen in this patient subset. The US Intergroup Trial Preliminary results of a US Intergroup trial also examining the use of rituximab and CHOP in elderly patients (age ≥ 60 years) with newly diagnosed advanced-stage DLBCL were presented at the American Society of Hematology (ASH) annual meeting in 2003,[38] and updated at ASH 2004.[39] This study had a double randomization design and compared induction therapy with CHOP vs R-CHOP followed by maintenance rituximab vs observation for responding patients. Rituximab maintenance was administered as four infusions every 6 months for 2 years. This study differed from the GELA trial in that rituximab was administered on a different schedule (two doses prior to starting CHOP, then with every other cycle of CHOP); patients received six to eight cycles of CHOP according to the response observed after four cycles; and half of responding patients received maintenance therapy with rituximab. A total of 546 patients were evaluable for induction and 352 for maintenance. Overall response rates were not different for R-CHOP (79%) vs CHOP induction (76%) (P = .92). With a median follow-up time of 3.5 years, time to treatment failure favored R-CHOP induction (53% vs 46% at 3 years, P = .04), but no survival advantage was seen. Regarding maintenance, patients receiving rituximab had a significantly prolonged time to treatment failure (P = .009), but no difference in overall survival. The time to treatment failure was prolonged with maintenance rituximab after CHOP (P = .0004) but not after R-CHOP (P = .81), demonstrating that there was no apparent benefit for maintenance rituximab if patients had received R-CHOP induction. However, this also confirmed that the use of maintenance rituximab confounded the induction analysis. In an attempt to eliminate the interaction between induction and maintenance, the authors performed two secondary analyses. A weighted analysis (excluding patients who received maintenance rituximab) demonstrated that the addition of rituximab to CHOP induction resulted in both a significantly improved time to treatment failure (52% vs 39% at 3 years, P = .003) and overall survival (67% vs 58% at 3 years, P = .05), confirming results of the GELA trial. A four-arm analysis of responding patients entering the second randomization demonstrated that time to treatment failure was significantly better in patients who had received rituximab at any time during their course of therapy, and suggested that the addition of rituximab to CHOP had an additive, rather than synergistic, effect. The British Columbia Population Analysis Based on initial encouraging results of the GELA trial, on March 1, 2001, the British Columbia Cancer Agency implemented a new provincial policy recommending the use of R-CHOP for all newly diagnosed patients with advanced stage DLBCL, regardless of age. A population-based retrospective analysis was performed, comparing outcomes in patients treated with a CHOP-like regimen with curative intent over an 18-month period prior to the introduction of rituximab (pre-rituximab) and the 18 months following (post-rituximab) the policy change.[40] A total of 294 patients were identified (142 pre-rituximab, 152 post-rituximab) using three independent data sources: the British Columbia Provincial Cancer Registry, British Columbia Cancer Pharmacy records, and the Lymphoma Clinical Database. Clinical characteristics were similar in both groups. The median age was 63 years (range: 19-86 years) with no differences in distribution of IPI scores. Patients received rituximab with each cycle of CHOP at the standard dose of 375 mg/m². Although the policy implementation date was March 1, 2001, 9% of the pre-rituximab patients received rituximab with chemotherapy and 15% of the post-rituximab patients did not receive rituximab. Results were analyzed based on the intended policy implementation date. Median follow-up was 34 months for the pre-rituximab patients and 17 months for post-rituximab patients. At 2 years, both the progression-free survival (71% vs 52%, P = .0009) and overall survival (77% vs 53%, P = .0001) were significantly improved in the post-rituximab group (Figure 2). An improvement in overall survival was seen in both younger (age < 60 years) and older (age ≥ 60 years) patients (Figure 3). In a multivariate analysis controlling for age, B symptoms, and IPI score, the era of treatment remained a strong, independent predictor of outcome for both progression-free and overall survival. This study confirmed results of the GELA and Intergroup trials and demonstrated the profound impact of the addition of rituximab to CHOP when administered to an unselected population of patients with DLBCL in routine clinical practice. This study was also the first to report a benefit of combined chemotherapy and rituximab for younger patients with DLBCL.
The MInT Trial The MabThera International Trial (MInT) evaluating CHOP-like chemotherapy with or without the addition of rituximab in young patients (age ≤ 60 years) with a favorable prognostic profile (IPI score 0 or 1) has recently been reported. The first complete analysis of 823 evaluable patients was presented at ASH 2004.[41] As in the GELA trial, the addition of rituximab resulted in a higher response rate and a lower rate of progression. With a median follow-up of 22 months, both 2-year time to treatment failure (76% vs 60%, \( P < .00001 \)) and 2-year overall survival (94% vs 87%, \( P < .001 \)) were significantly improved in patients who received rituximab. The combined weight of these three randomized studies, together with the British Columbia population analysis, confirms the substantial benefit of combination therapy and has established CHOP and rituximab as the new standard of care for all patients with advanced-stage DLBCL. While the above studies primarily targeted patients with advanced-stage disease, Miller and colleagues have recently reported results on 62 evaluable patients with limited-stage DLBCL treated with four cycles of rituximab added to the standard three cycles of CHOP and radiation therapy.[42] With a median follow-up of 2.4 years, progression-free and overall survival measured at 2 years were 94% and 95%, respectively. Outcomes were compared to a historical group of patients (\( n = 68 \)), with similar characteristics treated in a prior SWOG study of three cycles of CHOP and radiation therapy. The 2-year progression-free survival seemed more favorable in patients who received rituximab (94% vs 85%), suggesting a benefit of rituximab in patients with limited-stage disease. Secondary Therapy The PARMA trial established HDT and stem cell transplantation as the treatment of choice for aggressive lymphoma patients (< 60 years) with chemosensitive disease in first relapse.[43] This trial compared a standard salvage chemotherapy regimen, DHAP (dexamethasone, cisplatin,
cytarabine), with HDT and demonstrated a survival advantage in favor of HDT (53% vs 32% at 5 years, \( P = .038 \)). A variety of such secondary or salvage chemotherapy regimens have been used prior to transplantation or for patients who are transplant ineligible. No comparative trials of salvage regimens have been performed and therefore no consensus exists regarding the optimal regimen. Recent studies incorporating rituximab with a variety of standard salvage regimens have demonstrated high response rates.[44] Kewalramani and colleagues compared patients treated with R-ICE (rituximab with ifosfamide, carboplatin [Paraplatin], etoposide) (n = 36) to a historical group of similar patients treated with ICE alone (n = 147) prior to HDT.[45] Patients in the R-ICE cohort had higher response rates (CR rate 53% vs 27%, \( P = .01 \)), a trend toward improved progression-free survival (54% vs 45%, \( P = .25 \)), but no difference in overall survival. None of the patients in this study had received rituximab with first-line treatment. Therefore, the value of rituximab with salvage therapy in patients who have failed a combination of chemotherapy and rituximab up front remains unknown. Rituximab has been used prior to HDT and stem cell transplantation (as an in vivo purging agent), as well as after HDT to eradicate minimal residual disease. A recent phase II study investigating the use of post-transplantation rituximab in aggressive NHL yielded encouraging results (2-year event-free survival 83%; 2-year overall survival 88%).[46] Ongoing randomized trials will help to clarify choice of salvage chemotherapy and the role of rituximab in conjunction with HDT for relapsed patients.

**PET Scanning** The utility of 18FDG-positron emission tomography (PET) scanning in the assessment of aggressive NHL has been well demonstrated.[47] PET scanning is a functional imaging technique that allows the differentiation of benign from malignant tissue based on glucose uptake. It has been shown to be a more sensitive and specific radiologicmodality than CT scanning. However, there are no data demonstrating that an improved outcome results from the routine use of PET scanning for staging of aggressive NHL. PET scans performed following completion of treatment for NHL have been shown to be highly predictive of outcome. Spaepen and colleagues evaluated the utility of post-treatment PET scans in 93 patients with NHL.[48] All 26 patients with a positive PET scan following therapy went on to relapse, whereas only 11 of 67 patients (16%) with a negative PET scan relapsed. There was a highly significant association between PET scan results post-treatment and progression-free survival (\( P < .00001 \)). Early restaging PET scanning performed after one to four cycles of therapy has also been shown to be highly predictive of outcome.[49,50] In a prospective trial, 70 patients with aggressive NHL underwent PET scanning after three/four cycles of doxorubicin-based chemotherapy. None of the 33 patients with a positive midtreatment PET scan achieved a durable CR, whereas 31 out of 37 (84%) patients with a negative midtreatment PET scan remain in remission. In multivariate analysis, PET scanning at midtreatment was a stronger prognostic factor for progressionfree survival (\( P < .0000001 \)) and overall survival (\( p < .000009 \)) than the IPI. These results demonstrate that PET scanning is a powerful tool for assessing response to therapy in aggressive lymphoma, and will become increasingly used to guide treatment planning.

**Newer Therapies** While the addition of rituximab has been a major advance in the management of aggressive NHL, newer therapies are needed and many are under active investigation. Newer monoclonal antibodies are being evaluated. Alemtuzumab (Campath), an anti-CD52 humanized monoclonal antibody routinely used in chronic lymphocytic leukemia, has shown limited utility in aggressive lymphomas, with the exception of peripheral T-cell lymphoma.[51] Fully humanized anti-CD20 monoclonal antibodies targeting a different epitope on the CD20 molecule than rituximab have shown initial promise in early phase trials for lymphoma.[52] Epratuzumab, an anti-CD22 humanized monoclonal antibody, has been primarily evaluated in indolent lymphoma. A recent dose-finding study performed in aggressive NHL demonstrated some clinical utility with an objective response rate of 10% to 15%.[53] Bevacizumab, a humanized monoclonal antibody directed against vascular endothelial growth factor, is undergoing evaluation in early-phase trials in conjunction with R-CHOP for DLBCL.[54] Two radioiodinated anti-CD20 monoclonal antibodies (tosilumomab and ibrutumomab tiuxetan) have been approved for the treatment of relapsed follicular and transformed lymphoma.[55,56] These agents are under active investigation as part of conditioning therapy for autologous transplantation and following R-CHOP chemotherapy for aggressive lymphoma. Numerous chemotherapeutic agents and targeted molecules are being actively investigated. Bcl-2 antisense has shown evidence of activity in NHL.[57] and trials are under way in combination with R-CHOP for newly diagnosed aggressive lymphoma. Bortezomib (Velcade) has shown promise in mantle cell lymphoma, but only limited data are available regarding its utility in other aggressive lymphomas. In a recent study, only one partial response was observed in 12 patients treated with bortezomib for relapsed or refractory DLBCL.[58] Gene array studies have identified overexpression of PKC-b to be associated with a poorer prognosis in DLBCL.[6] Trials investigating agents that target this enzymatic pathway have recently been initiated. **Conclusions** Advances in molecular biology...
have allowed an increased understanding of the heterogeneity of NHL, including aggressive histologies such as DLBCL. The addition of rituximab has been the first major improvement in therapy in 2 decades for patients with this aggressive lymphoma. However, the pace of further improvement is likely to be much more rapid. The insights from powerful new molecular techniques such as gene expression profiling should permit identification of additional lymphoma specific therapeutic targets. Newer chemoimmunotherapeutic agents, such as proteosome inhibitors, histone deacetylase inhibitors, and novel monoclonal antibodies, are already being tested in phase II clinical trials. The potential of radioimmunoconjugates has yet to be fully realized. Integration of functional imaging techniques such as PET scanning into therapeutic decision-making has major potential to alter current treatment algorithms. Further advances identifying newer targeted agents that take into account underlying biology and allow for greater tailoring of therapy will almost certainly result from these novel approaches. The key to rapid translation of these new techniques into routine patient management will remain the proper design and conduct of innovative clinical trials that will continue to deserve the wide support of North American oncologists.

Disclosures:
Dr. Sehn and Dr. Connors have received research sponsorship from and acted as consultants to Hoffman La Roche (Roche Canada).

References:


Source URL:
http://www.cancernetwork.com/oncology-journal/treatment-aggressive-non-hodgkin%E2%80%99s-lymphoma-north-american-perspective

Links:
[1] http://www.cancernetwork.com/review-article
[2] http://www.cancernetwork.com/oncology-journal
[4] http://www.cancernetwork.com/authors/laurie-h-sehn-md-mph
[5] http://www.cancernetwork.com/authors/joseph-m-connors-md