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NON-HODGKIN'S LYMPHOMA

Update on lymphoma management: Diffuse large B-Cell NHL

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring subtype of non-Hodgkin's lymphoma (NHL) in the Western Hemisphere, comprising about one-third of all adult lymphomas [1]. The natural history of this subtype is aggressive, with a median survival of less than 1 year in untreated patients. Over the past decade, remarkable progress has been made in understanding the biological heterogeneity of DLBCL. There is clear evidence that, in many cases, the clinical behavior of certain DLBCLs can be profiled by the expression of molecular markers [2,3]. These markers have not only contributed to the development of novel prognostic models, allowing clinicians to refine their ability to identify patients at high risk but they have also been integral in the identification of new therapeutic targets.

The clinical management of DLBCL has changed dramatically over the past five 5 years. Routine incorporation of monoclonal antibody therapy in induction treatment regimens has improved OS in most subgroups of patients with DLBCL. In addition, studies evaluating high-dose chemotherapy and autologous stem cell transplantation (SCT) as consolidation treatment during first remission have shown promise. Perhaps most exciting is the multitude of promising new agents now under development.

Despite many recent advances, most patients with advanced-stage DLBCL are not cured with conventional therapy. Given this reality, treating physicians must recognize the inadequacy of current therapies and urge their eligible patients to participate in well-designed clinical trials. The development of novel therapies may result in improved outcomes for patients diagnosed with these common NHL subtypes.

Diffuse large B-Cell lymphoma–clinical risk stratification

Clinical risk stratification is necessary to define optimal therapy for patients with "early stage" DLBCL. "Early stage" NHL usually refers to disease limited to a single side of the diaphragm, including, at most, stage 1 contiguous extranodal site. It has been well documented that patients with "bulky" stage 2 disease (i.e., a mediastinal mass >10 cm or $>1/3$ of the maximum diameter of the chest) have a prognosis indistinguishable from that of patients with advanced-stage disease; thus, these patients should be treated differently from other patients with early-stage disease.

Randomized clinical trials have demonstrated that a combined-modality approach incorporating a brief duration of chemotherapy followed by involved-field radiation remains a reasonable standard of care for most patients with early stage DLBCL. A SWOG study randomized 401 patients with aggressive *non-bulky* stage 1 or 2 NHL (mainly DLBCL) to 3 cycles of CHOP followed by involved-field radiation (40–50 Gy) or to 8 cycles of CHOP alone [4]. At 5 years, PFS and OS rates were significantly higher in the combined-modality arm than in the chemotherapy-alone arm (77% vs. 64% and 82% vs. 72%, respectively, with less life-threatening toxicity in the combined modality arm ($P=0.06$).

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More recently, the Eastern Cooperative Oncology Group (ECOG) enrolled 210 patients with either diffuse, aggressive stage 1 lymphoma with mediastinal or retroperitoneal masses greater than 10 cm in diameter (bulky disease), or stage 1E, 2, or 2E disease. The 172 patients who had attained CR after 8 cycles of CHOP were randomized to receive no further therapy or involved-field radiation [5]. Disease-free survival at 6 years was superior in the combined treatment arm (73% vs. 56%; 2-sided $P = 0.05$). However, there was no difference in overall survival. Therefore, the benefit of radiation therapy following a full course of chemotherapy appears to be limited to enhanced local control.

When any risk factor (age >60 years, high lactate dehydrogenase (LDH) level, stage 2 disease, and performance status ≥ 2) by the stage-modified ("Miller Modification") International Prognostic Index (IPI) is present, outcome is inferior to that of patients with no risk factors [6]. For example, in the SWOG study, 5- year overall survival was 94%, 71% and 50%, respectively, for those with 0 or 1, 2, or 3 risk factors; and 5-year failure free survival estimates were 82% for patients with 0 or 1 risk factor, 71% for patients with 2 risk factors, and 48% for patients with 3 risk factors [4]

These findings have been confirmed by Canadian researchers who evaluated combined modality therapy in a similarly defined group of early stage patients [7]. The overall survival rates at 5 years were 97% for patients with no risk factors, 77% for patients with 1–2 risk factors, 58% for patients with 3 risk factors, and 48% for patients with 4 risk factors, with similar decrements in PFS reported for increasing numbers of risk factors [7].

Similarly, in the ECOG study, the following factors were significantly associated with prolonged survival among patients receiving induction CR: age less than 60 years ($P < 0.001$), and fewer than 3 disease sites ($P = 0.01$). As in the Canadian trial, these factors were also associated with prolonged survival among complete responders receiving induction therapy [5].

The Groupe d'Étude des Lymphômes de l'Adulte (GELA) has reported results from a randomized trial of previously untreated patients younger than 61 years with localized, aggressive stage 1 or 2 lymphoma and no IPI risk factors. The study compared 3 cycles of CHOP plus involved-field radiotherapy (n = 329) or chemotherapy alone with dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) plus sequential consolidation with high-dose methotrexate, etoposide, ifosfamide, and cytosine arabinoside (n = 318) [8]. Notably, patients with bulky stage 2 disease were not included in this trial. The 5-year event-free survival estimates were 82% for patients receiving ACVBP chemotherapy alone (followed by intensive consolidation) and 74% for those receiving standard CHOP with radiation therapy. The respective 5-year OS estimates of OS were 90% and 81%, respectively. Thus, ACBVP conferred only a modest survival benefit among patients without bulky disease.

The GELA group presented data from an early analysis of elderly patients with localized aggressive NHL and an age-adjusted IPI risk of 0 [9]. The report suggested that the adding involved-field radiotherapy to 4 courses of CHOP did not improve CR rates, 5-year event-free survival, or 5-year OS [23]. Finally, another preliminary report from a SWOG pilot trial that treated patients with limited stage disease to 3 cycles of R-CHOP, followed by radiation therapy [10] calculated 2-year progression-free survival and OS at 94% and 95%, respectively, superior to historical results with CHOP chemotherapy alone. Of note, this trial required patients to have at least 1 risk factor in the Miller IPI modification. However, 10-year follow-up of SWOG's original randomized trial [11] suggested an increase in late recurrences (>5 years after completion of therapy) in patients treated with combined radiochemotherapy, including a fixed mortality rate over the first 10 years, with no evidence of a plateau in the survival curve. Therefore, long-term follow-up is clearly required before it can be said that one regimen is superior to another, particularly when that regimen is compared with historical controls.

Despite the preliminary nature of these follow-up findings, the SWOG investigators currently recommend 3 cycles of CHOP plus rituximab in addition to involved-field radiation for most patients with stage 1 and nonbulky stage 2 disease, on the basis of increased survival through the first 9 years and less associated toxicity. Select elderly patients lacking other risk factors may not require radiation therapy, and patients with bulky disease clearly require more chemotherapy and may benefit from intensified regimens. By using new approaches such as radioimmunotherapy and 18F-fluorodeoxyglucose positron emission tomogram imaging, current clinical trials in patients with early stage DLBCL and at least 1 Miller IPI modification risk factor [12] will be useful in defining which patients may not require external-beam radiation.

In patients with advanced-stage DLBCL, rituximab appears to improve survival when administered in combination with standard chemotherapy, but no additional benefit is observed with the addition of maintenance rituximab.

In a 2002 publication, GELA reported that rituximab added to standard CHOP conferred a higher OS rate for older patients (>60 years) with advanced-stage DLBCL [13]. These results truly changed clinical practice throughout much of the world. Eight cycles of CHOP alone (control arm) or CHOP with rituximab (treatment arm) produced CR rates of 63% and 76%, respectively ($P = 0.005$) and a 2-year OS of 57% and 70% ($P = 0.007$). A recent update of this

trial demonstrated that the survival benefit was maintained, and actually continued to improve through 5 years of follow-up [14]. A subgroup analysis of this large study has revealed that 2 groups of patients appear to derive particular benefit from rituximab: (1) those with an age-adjusted low IPI risk and (2) those with DLBCL positive for Bcl-2 overexpression, historically a poor prognostic factor. This finding suggests that one of the ways in which rituximab works is to overcome Bcl-2-associated chemotherapy resistance [15].

Preliminary results from the MabThera International Trial (MInT), currently evaluating CHOP-like chemotherapy regimens plus rituximab in patients younger than 60 years, were recently presented [16]. As in the GELA trial, patients who received rituximab plus chemotherapy had a significantly longer 2-year time to treatment failure (81% vs. 58%) than patients receiving chemotherapy alone. In addition, the 2-year OS rates also significantly favored chemotherapy plus rituximab (95% vs. 85%).

Similar to the GELA trial, the as-yet unpublished larger (N = 632) US Intergroup Study randomized a population of 632 elderly patients to 8 cycles of CHOP or CHOP plus rituximab given every other cycle [17]. Responding patients were then randomized to receive either rituximab "maintenance" (4 doses, every 6 months for 2 years or no maintenance therapy. A weighted analysis was used to mathematically model the groups that had been treated with CHOP alone or CHOP plus rituximab as induction therapy, controlling for maintenance exposure. The magnitude of the OS benefit of induction therapy with CHOP plus rituximab was similar to that seen in the GELA trial, which essentially confirmed the GELA results. Perhaps the most important contribution of the United States Intergroup Study, however, was that it demonstrated a lack of benefit with "maintenance" rituximab when rituximab was included in the initial chemotherapy regimen.

The role of dose-intense regimens which are rituximab-based therapies is unclear. Recently published results of 2 large German trials (NHL-B1 and NHL-B2) suggest that modifications to the CHOP regimen may improve survival. The major limitation of these trials is that they did not include rituximab. These 2 trials randomized patients to 6 cycles of CHOP-21 (every 3 weeks) or CHOP-14 (every 2 weeks) vs. CHOEP-21 (CHOP plus etoposide 100 mg/m^2 Days 1–3 every 3 weeks) or CHOEP-14 (CHOP plus etoposide 100 mg/m^2 Days 1–3 every 2 weeks). Patients in these trials also received radiotherapy (36 Gy) to both extranodal and bulky disease sites. One trial (NHL-B2) was limited to patients older than 60 years [18]. Five-year event-free and OS rates were respectively 32.5% and 40.6%, for CHOP-21 and 43.8% and 53.3% for CHOP-14. Toxicity was similar among CHOP-14 and CHOP-21 participants, but CHOEP-21, and, especially, CHOEP-14 were more toxic than either CHOP regimen. In the parallel trial (NHL B1) for patients younger than 61 years, better complete remission rates were obtained with CHOEP than with CHOP (87.6% vs. 79.4%; $P = 0.003$) as well as improved 5-year event-free survival rates (69.2% vs. 57.6%; $P = 0.004$, primary end point) [19] The benefit of interval reduction was less clear in the younger than in the older patients. Although the CHOEP were more myelosuppresive, they were reasonably well tolerated. Only 3 therapy-associated deaths occurred, 1 (0.5%) among the CHOEP-21 and 2 (1.1%) among the CHOEP-14 participants.

The magnitude of benefit seen with these dose-intense regimens is similar to that observed with the addition of relatively nontoxic rituximab therapy reported in other trials. Indeed, a recent retrospective analysis of patients included in the MInT trial suggests that survival differences between different CHOP-like regimens, including CHOEP, disappear when rituximab is added to standard therapy [20]. Since trials incorporating monoclonal antibody therapy into these dose-intensified regimens are ongoing, the routine use of dose-intense regimens outside of a clinical trial is not currently recommended.

Ongoing prospective trials are underway to define the role of autologous stem cell transplantation (ASCT) consolidation for patients with high-risk, advanced-stage DLBCL in first remission.

Several phase 3 trials have evaluated ASCT in newly diagnosed patients with DLBCL, either as consolidation therapy after CR or as induction therapy. In most of these trials, however, high-risk disease was identified by criteria other than the IPI, and a variety of schedules incorporating ASCT have been used [21].

The Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang (GOELAMS) trial randomized 197 consecutive patients to receive either 8 courses of standard CHOP chemotherapy, or a complicated regimen of ASCT plus chemotherapy, starting with cyclophosphamide, vindesine, epirubicin, and prednisone (CEEP), followed by high-dose methotrexate and cytarabine, then treated with carmustine, etoposide, cytarabine, and melphalan (BEAM) for stem cell conditioning prior to ASCT [22]. Overall, 78% of the patients completed the assigned treatment. With a median follow-up of 4 years, the estimated event-free 5-year survival rate was significantly higher for patients who received ASCT than for those who received standard CHOP (55% vs. 37%). A retrospectively performed subgroup analysis demonstrated a survival benefit in patients with age-adjusted high-intermediate IPI risk (OS, 74% vs. 44%).

These data are reminiscent of the LNH87–2 trial results previously published by GELA [23]. In this trial, 1043 patients were initially randomized to

treatment with 4 courses of an anthracycline-based regimen. Patients who achieved CR were randomized to receive additional cycles of sequential chemotherapy or ASCT. As in the GOELAMS trial, a retrospective assessment of 451 high-intermediate or high IPI risk patients showed that the 8-year OS rate was higher in the ASCT arm than in the sequential chemotherapy arm (64% vs. 49%). Of course, these retrospective subgroups analyses must be interpreted cautiously because these higher risk patients were not initially identified as the target population for these trials. Most of the current mature phase 3 trials have reported improved disease-free survival (DFS) but not improved OS with ASCT therapy in patients younger than 60 years with high or high-intermediate IPI risk scores [21]. Moreover, none of these trials included rituximab therapy, so it is not known whether the benefit of is abrogated by the addition of rituximab to induction or consolidation therapies. This is a particularly important question in light of the MInT trial analysis, suggesting that rituximab may abrogate the benefit of intensified regimens.

Radioimmunotherapy with iodine-131 (I-131) tositumomab or ibritumomab tiuxetan is quite active in the treatment of indolent B-cell lymphoma and is worthy of further investigation in other lymphoma subtypes. Zelenetz and colleagues analyzed 71 patients whose indolent lymphomas underwent Richter's transformation to more aggressive histologic forms who were treated with I-131 tositumomab in 5 clinical trials [24]. The overall response rate for a single treatment with I-131 tositumomab was 39%, with a median response duration of 20 months. In 24% of these patients, response duration was longer than 1 year. Given the relatively low toxicity profile of the I-131 tositumomab regimen compared with that of ASCT, [25] the radioimmunotherapy approach holds significant promise for patients with transformed disease.

Morschhauser and colleagues have recently completed a prospective, multicenter phase 2 trial to evaluate the efficacy and safety of yttrium-90 ibritumomab tiuxetan in elderly patients with histologically confirmed primary refractory or relapsed DLBCL for whom ASCT is contraindicated [26]. An overall response rate of 44% was observed for the entire study population. The median response duration was 22 months in those patients who had never received rituximab. By contrast, only 19% of patients treated with prior chemoimmunotherapy responded to radioimmunotherapy.

These results are encouraging. Both I-131 tositumomab and yttrium-90 ibritumomab tiuxetan are currently being evaluated for the treatment of DLBCL in multicenter trials. For example, SWOG is currently conducting a trial with I-131 tositumomab as consolidation therapy following standard R-CHOP for patients over 60 with DLBCL.

Despite the many recent advances summarized in this manuscript, most patients with advanced stage DLBCL are not cured with conventional therapy, Hence, each treating physician must recognize the inadequacy of current therapy and urge all eligible patients to participate in well-designed clinical trials. Several of the investigators conducting ongoing clinical trials have emphasized that providing optimal therapy often involves experimenting with both new and old agents in novel ways. Further development of the aforementioned novel therapies should result in improved outcomes for patients suffering from these common subtypes of NHL.

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