Managing large cell lymphoma

C. Gisselbrecht* & N. Mounier
Institute for Hematology, Hôpital Saint Louis, Paris, France

Rituximab has greatly improved standard cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy, but prospects remain poor in patients with adverse risk factors. We need to know whether the addition of rituximab also improves the efficacy of more intensive treatments and how to use molecular profiling to guide us in introducing other novel agents.

Key words: large cell lymphoma, risk factors, rituximab, chemotherapy, autologous stem cell transplantation

introduction
Understanding and treatment of aggressive lymphomas have undergone continuous progress. The permanent change in classification has been solved by a recognized histological WHO classification [1] which will evolve with molecular biology findings. The classical chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) has been challenged by several randomized studies, either by increasing dose or dose intensity or by the addition of monoclonal antibodies such as rituximab. The definition of clinical prognostic factors through the international prognostic index (IPI) has been efficient in tailoring therapy for poor prognosis patients.

how to define a poor prognosis lymphoma?
These patients have generally two or more IPI prognostic factors where the complete response rate does not exceed 65% with a 5-year probability of survival of less than 50%. Within this group sharing the same adverse factors, it has been showed that several parameters will influence the outcome. A clear distinction that is useful for the treatment has been made between the T non-anaplastic lymphoma of worst prognosis, T anaplastic lymphoma and B large cells lymphomas (DLBCL) [2]. More recently using micro arrays, it has been possible to demonstrate in diffuse large B cell lymphoma that within a clinical group defined by IPI, the distinction between germinal center B cells (GCB) and the activated peripheral blood peripheral B cells (ABC) could further stratify the patients for overall survival [3]. All prognostic markers in lymphoma are subject to the influence of therapy. The prognostic importance of Bcl-2 protein expression as a predictor of inferior survival in patients with DLBCL has been reported. When patients were treated with rituximab and CHOP the negative impact of Bcl-2 expression was overcome [4]. The introduction of novel biomarker assessment in DLBCL may soon be at the level of routine immunohistochemistry. The definition of poor prognosis lymphoma will be described further in the future and more targeted treatment will emerge from this research work.

progress in treatment before the rituximab era
The results of CHOP established this regimen as a standard for several decades. However, with a projected disease-free survival rate of 36%, it is not an ideal treatment and there is a need for better treatment approaches especially in poor prognosis lymphoma.

Before the rituximab era, three European randomized studies demonstrated the superiority of intensive chemotherapy when compared with CHOP. In localized stage without adverse prognostic factor [5], the intensive regimen of doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) [6] was compared with three cycles of CHOP chemotherapy followed by involved field irradiation. In patients less than 60 years of age with a median follow-up of 7.7 years, there was superiority in survival (90%) and event-free survival (82%) for the 318 patients treated with ACVBP when compared with the survival (81%) and event-free survival (74%) of the 329 patients treated with CHOP and radiotherapy. In multivariate analysis, survival rates were affected by treatment arm but not by the presence of bulky disease. The place of radiotherapy has been considerably reduced with this intensive regimen associated, nevertheless, with severe but manageable toxicities.

This was also true for patients with adverse prognostic factors as demonstrated in a randomized trial in which we compared the ACVBP chemotherapy regimen with standard CHOP [7]. Patients aged 61–69 years who had aggressive non-Hodgkin’s lymphoma with at least one adverse prognostic factor (advanced stage, poor performance status or elevated LDH level) were randomly assigned to receive ACVBP or
investigators have reported impressive results on the use of autologous stem cell transplantation (ASCT) as consolidation therapy for DLBCL poor-prognosis patients.

Four randomized trials [9–12] have provided positive information on the role of ASCT in patients with adverse prognostic factors. In the LNH87-2 study [9], 1043 patients with various adverse prognostic factors were enrolled. Complete remission was achieved in 614 patients, who were then randomized to receive either intensive consolidation with ASCT or sequential chemotherapy. There was no difference in overall survival or disease-free survival between the two consolidation arms. However, for the subgroup of 236 patients with at least two adverse IPI factors, ASCT had a significant advantage in terms of 8-year disease-free survival (55% versus 39%, P = 0.01) and in survival (64% versus 39%, respectively, P = 0.04).

The absence of consensus on prognostic factors for patients treated with consolidate ASCT increases the difficulty of comparing studies or designing clinical trials on maintenance therapy. We aimed to estimate the prognostic effect of clinical and biological variables by pooling the data from GELA trials on up-front ASCT [13]. Patients less than 60 years old and in complete remission received ASCT after induction ACVBP regimen, as in the LNH87 study. Among 330 patients, the median age was 43 years. Age-adjusted IPI score was equal to 0 in 11%, 1 in 23%, 2 in 51% and 3 in 15%; 140 patients (43%) had more than one extra-nodal site and 69 had marrow involvement. The histological slides showed: B aggressive non-Hodgkin’s lymphoma (NHL) in 249 patients (75%), T NHL in 52 patients (including 23 T anaplastic) and non-classified NHL in 29 cases. With a median follow-up of 6.5 years, the 5-year OS was 75% and EFS was 67%. The univariate analysis showed that age-adjusted IPI (0–1 versus 2–3) had no prognostic value (5-year OS 76 versus 74%, P = 0.48; EFS 65 versus 66%, P = 0.67). In multivariate analysis the following parameters had a significant (P < 0.05) adverse effect: age >35 years old, marrow involvement, number of extra-nodal sites >1 and histology (non-anaplastic T versus others).

A complementary pair-matched analysis from the same GELA database (on histology, phenotype, extranodal sites, marrow and anthracycline) with control patients treated with ACVBP induction and sequential consolidation chemotherapy confirmed the poor prognosis of non-anaplastic T NHL (5-year OS 44% (chemotherapy) versus 49% (ASCT), P = 0.87; EFS 38% versus 45%, P = 0.89).

This cohort study confirms the high efficacy of upfront ASCT in NHL responding patients. Our results suggest that ASCT is able to prevent chemotherapy failure in patients with adverse age-adjusted IPI factors. However, patients presenting with T phenotype or more than one extranodal site still have a higher risk of relapse.

progress in the treatment with rituximab

Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and has activity in relapsed or refractory diffuse large-B-cell lymphoma (DLBCL).
Randomized studies demonstrated in DLBCL that CHOP plus rituximab increase CR rate, EFS and overall survival. Factors affecting response are low IPI, Bcl2 oncoprotein overexpression.

The GELA completed the first study to compare CHOP plus rituximab with CHOP alone in elderly patients with DLBCL [14]. Previously untreated patients with DLBCL, 60–80 years old, were randomly assigned to receive either eight cycles of CHOP alone (197 patients) or eight cycles of CHOP plus rituximab given on day 1 of each cycle (202 patients). The rate of complete response was significantly higher in the group that received CHOP plus rituximab than in the group that received CHOP alone (76% versus 63%, P = 0.005). Updated results with a 5-year median follow-up confirm this benefit [15]. The OS estimate for all patients was 52% ± 6%. OS was significantly longer for the 137 patients treated with R-CHOP than for the remaining 155 treated with CHOP alone (OS 57% ± 8% versus 45% ± 9%, P = 0.02; EFS 47% ± 9% versus 25 ± 8%, P < 0.0001).

The OS curves confirmed that R-CHOP was significantly associated with a better OS than CHOP in 193 bcl-2-positive patients (56% ± 9% versus 42% ± 11%, P = 0.01), whereas in 99 bcl-2-negative patients there was no statistically significant difference (58% ± 14% versus 52% ± 15%, P = 0.6). The same results were found for EFS (bcl-2-positive, 46% ± 11% versus 21% ± 9%, P = 0.0001; bcl-2-negative, 49% ± 13% versus 31% ± 13%, P = 0.06). As in DLBCL patients, deaths during the first 2 years mostly reflect treatment failure, rituximab significantly decreases the risk of progression or relapse in both bcl-2-positive (RR = 2.6, P = 0.001) and bcl-2-negative (RR = 2.2, P = 0.01) patients. Results from the MINT study [16] demonstrated the benefit of R-CHEMO for all patients irrespective of these risk factors. However, 2-year TTF after R-CHEMO in patients with bulky disease and/or IPI = 1 was significantly worse (P < 0.001) than in patients with IPI = 0 and no bulk (71% versus 90%, respectively). While further improvement will be difficult to demonstrate for the favorable (IPI = 0, no bulk) subgroup, it is still warranted with regard to TTF for the less favorable subgroup (IPI = 1 and/or bulk).

In this study, results with R-CHOP are similar to R-CHOEP. Several randomized studies are ongoing exploring the association of rituximab with other regimens: CHOP/14, ACVBP, DA-EPOCH. Nevertheless, improving the CR rate remains the major goal for these high-risk patients. It is not known if the addition of rituximab in a more intensive regimen for poor prognosis lymphoma will increase the CR rate. The long-term results of the R-CHOP regimen did not show a significant advantage of survival for this group of patients. It seems probable that a group of poor prognosis patients exists who would benefit from high-dose therapy in first remission. The incorporation of rituximab in a more intensive regimen could improve the results. The other use of rituximab could be as maintenance after transplantation in order to reduce the relapse rate. Since, at present, the evidence base is not sufficiently substantial, entry into ongoing trials should be encouraged, but patients in first remission should be offered the option of high-dose therapy.

From these experiences, it is clear that NHL remain sensitive to chemotherapy after relapses. However, the duration of response will depend not only on the quality of salvage regimen but on several factors: time to relapse, on/off therapy, prior treatment, secondary IPI. A further uncertainty is the way prior exposure to the antibody may compromise the chances of response to salvage following a relapse [14]. Results should be interpreted with these parameters. In NHL large prospective studies with new combination chemotherapy with rituximab are necessary to establish some standard for salvage chemotherapy.

The increasing use of PET scanning during early chemotherapy allows one to assess the biological response and to predict risk of relapse. Patients who are PET-negative after two cycles have much better event-free survival at 2 years than patients who are PET-positive during early treatment [17]. PET scanning will join the list of clinical, immunohistochemical and molecular features of disease that enable us to target novel therapies most in need of them.

references


