Abstract

High dose therapy with autologous stem cell transplantation (ASCT) has been widely used in the past decade for treating aggressive non-Hodgkin's lymphoma in situations in which conventional therapy was not likely to cure patients. In patients achieving complete remission, ASCT has been proposed for consolidation in a group of lymphoma patients sharing adverse prognostic factors with a high risk of relapse. Results from pilot studies were encouraging. Analysis of the large randomized LNH87 trial, showed an increased survival and disease free survival advantage for ASCT performed after CR when compared to conventional chemotherapy if patients with 2 or more adverse factors were included. For patients who do not achieve CR after conventional treatment, but who are still sensitive to chemotherapy, ASCT may improve results. Pilot studies as well as randomized studies offer support for this approach. Intensive treatment with ASCT has been reported in thousands of relapsing lymphoma patients. For those remaining sensitive to salvage chemotherapy at 5 years, a 40% probability of disease free survival has been uniformly noted. Moreover, these results were confirmed by the randomized PARMA study testing ASCT vs conventional chemotherapy. ASCT is accepted by most centers as the treatment of choice for relapsing lymphoma. For lymphoblastic lymphoma and Burkitt's lymphoma, the role of ASCT in first CR is not well defined, although results from pilot studies and the analysis of registry data support the use of ASCT in lymphoblastic lymphoma with adverse prognostic factors. In conclusion, data supporting the use of ASCT in lymphoma in different settings has been provided by numerous non randomized trials. Completed randomized studies clearly demonstrate a benefit for ASCT in most relapsing patients as well as a subset of patients with poor prognosis. Socio-economic implications of such results must be evaluated, especially since the development of peripheral hematopoietic stem cells will reduce both toxicity and cost.

In the past ten years, a considerable amount of effort has been devoted to evaluating whether intensive treatment will improve the outcome for patients with intermediate and high grade non-Hodgkin’s lymphomas (NHL). Despite promising results in pilot studies testing second and third-generation therapies, several carefully conducted clinical trials have demonstrated that none of the major regimens is convincingly better than CHOP [10, 14, 34]. These studies, however, compared multidrug combinations which, in fact, had the same dose-intensity as CHOP for the two major agents, adriamycin and cyclophosphamide. Several attempts were made to increase the dosage [8, 12] and randomized studies are now in progress to evaluate CHOP against a high dose CHOP regimen such as ACVB. For poor prognosis lymphoma, however, it is unlikely that a major improvement will be observed. In therapeutic studies the emphasis has now switched to the use of high-dose therapy followed by transplantation of autologous stem cells from peripheral-blood or bone marrow (ASCT). Pilot studies of high-dose therapy and ASCT showed that this therapy offers some potential for long-term survival in a limited number of chemosensitive relapses thought to be incurable using conventional therapy [3, 15, 30]. However, results from these studies may be misleading, since they are biased notably by the mode of selection of patients; such studies can in no way substitute for prospective comparative trials. Many questions remain unanswered concerning optimal management of lymphoma, and the role of recent
technological developments possibly offering new forms of treatment. This review will attempt to summarize the current situation by encompassing all available recent data.

**Upfront autologous stem cell transplantation**

The greatest challenge was to identify those patients who ought to be candidates for ASCT, because they were unlikely to respond to standard therapy or because their response would be of short duration. The International Non-Hodgkin's Lymphoma Prognostic Factors Project [36] has identified four risk groups based on five pre-treatment variables (age, stage, serum LDH, performance status and number of extranodal disease sites) thereby increasing the likelihood of choosing the optimal treatment for poor prognosis patients. For patients without adverse factors, the complete remission rate is 92% and the 5-year survival rate is 83%; these patients represent 22% of the studied population. For those patients with 2 adverse factors and those with more than 2 factors, the CR rates are 57% and 46%, and the 5 year survival rates are 46% and 32%, respectively. Such patients represent 46% of the population of aggressive NHL. This subset of patients are the best candidates for studying new strategies.

Several investigators have reported the use of high-dose therapy with autologous BMT as part of the primary therapy of patients with intermediate-grade NHL [2, 17, 27]. Recently, Pettengel et al [29] reported a retrospective comparison between standard and intensive treatment strategies for lymphoma patients presenting with two and three prognostic factors according to the international index. Thirty four patients received 11 weeks of doxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide, prednisolone and methotrexate (VAPEC-B), while 33 patients received intensive treatment with 7 weeks of VAPEC-B and three cycles of ifosfamide/cytarabine, followed by high-dose busulfan/cyclophosphamide and then autologous blood progenitor-cell support. At 2 years, the rates of event-free survival and overall survival significantly differed between the intensive and standard treatment groups (61 vs 35% and 64 vs 35%, respectively).

These authors concluded that the high-dose therapy approach in high-risk patients was promising but required confirmation using randomized trials. In 1987, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) designed a randomized study to evaluate the potential benefit of a high dose regimen followed by autologous bone marrow transplantation after complete remission. Induction treatment was that of the LNH84 protocol with an open randomization with respect to the anthracycline. After 4 cycles, over a period of 2 months, patients in complete remission were further randomly assigned to receive either sequential chemotherapy or autologous stem cell transplantation. Autologous stem cell transplantation was performed after a high dose regimen containing cyclophosphamide, carmustine and etoposide (CBV). Haioun et al [18] reported on 790 patients included in the initial randomization. With a median follow-up duration of 28 months, the 3-year disease-free survival rate was 52% in the sequential chemotherapy arm and 59% in the autologous transplantation arm (p = 0.46). The 3-year survival rate did not differ between sequential chemotherapy and autotransplantation, i.e. 71 and 69% respectively (p = 0.60). However, the population enrolled was somewhat heterogeneous. An updated analysis was carried out on 916 eligible patients using the International Index [19]. When applied to patients randomized for consolidation, there was no statistically significant difference between the two consolidation arms, in the low-risk group (0 factor, 110 patients) and in the low-intermediate and high risk group (1 factor, 312 patients). On the other hand, for the high-intermediate and high risk group (2-3 factors, 236 patients), the 5-year disease-free-survival rate was significantly higher in the ABMT arm when compared to chemotherapy (59 vs 39%; p = .01) as well as the 5-year survival rate (65 vs 52%; p = .06). From these different studies, we conclude that dose-intensive consolidation with ASCT should be proposed for patients who achieve complete remission after induction treatment if they have at least two adverse prognostic factors.

Several randomized studies addressing this question are currently in progress. In one of these, Gianni et al [11] developed early intensification with a novel high-dose chemotherapy regimen that takes full advantage of growth factor use. In a phase III trial, a high-dose regimen requiring hematopoietic progenitor cell autotransplantation was randomized with a third-generation chemotherapy regimen (MACOP-B) as the initial treatment for poor-risk non-Hodgkin's lymphoma. In the first interim analysis, 38 patients entered the high dose arm and 37 patients the MACOP-B arm. After a median follow-up of 43 months, the remission rate