Role of high-dose therapy in diffuse large B-cell lymphoma

Thomas Cerny [a] and Daniel Betticher [b]

[a] *Department Internal Medicine, Head of Oncology / Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland*
[b] *Institute of Medical Oncology, University of Berne, Inselspital, Berne, Switzerland*

Introduction

Diffuse large B-cell lymphoma is the most frequent Non Hodgkin's Lymphoma entity seen in the western world, over 30% of all cases. Furthermore, the disease incidence is increasing in most western countries. Although it is a curable disease most patients will eventually die due to disease accounting for relapse. Despite many attempts during the last three decades to increase the cure rate of 35 to 40%, we have not yet succeeded in improving the results significantly since CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy was introduced in the 1970s [1]. Second and third generation regimens as compared to the first generation CHOP failed to demonstrate an advantage over the CHOP regimen [2,3]. More recently, attempts to improve treatment outcome have focused on increasing the dose intensity of cytotoxic drugs by applying high-dose chemotherapy, with or without involved field or total body irradiation, supported by autologous haematopoietic stem cell transplantation. Autologous bone marrow and, more recently, autologous haematopoietic stem cells collected from peripheral blood after mobilisation from bone marrow have both been used to assure haematopoietic reconstitution after high-dose myeloablative chemotherapy. The availability of haematopoietic growth factors has facilitated both the mobilisation of haematopoietic stem cells into the peripheral blood and the application of high-dose chemotherapy programs [4–8]. Furthermore efficient purging procedures of stem cells before reinfusion is an other important step towards improving treatment results.

Important clinical and biological prognostic factors as well as molecular therapeutic targets have been identified and are instrumental in further improving our treatment strategy.

High-dose chemotherapy with autologous stem cell support in relapsed patients

The well-known Parma trial examined the value of autologous bone-marrow transplantation compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma [9]. Patients having relapsed after an initial complete remission and younger than 60 years with no evidence of CNS or bone marrow involvement were first treated with two courses of conventional salvage chemotherapy. Patients responding with at least a partial response (PR) were then considered to be chemosensitive and randomised to involved field radiotherapy and high-dose BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) chemotherapy versus DHAP (dexamethasone, high-dose Ara-C, cisplatin) chemotherapy for six additional months followed by involved field radiotherapy. The event-free survival was 46% for the high-dose arm compared to 12% patients with conventional salvage chemotherapy. There was also an advantage in overall survival for the high-dose therapy group. The conclusion was that high-dose therapy with stem-cell support is the treatment of choice for relapsed aggressive lymphoma patients using the criteria of the Parma study. These results have been confirmed in other trials and with other treatment regimens [10–15].

The European bone marrow transplant group (EBMT) has collected the data of patients treated in first or later relapse [16]. The most important prognostic factor seems to be sensitivity to chemotherapy. There is a group of patients who are in long-term remission but we do not have a detailed understanding of which factors other than sensitivity to salvage therapy and bulk of disease are the most important in predicting beneficial or deleterious outcome.

Although patients with a chemosensitive relapse have a chance of cure no such results are obtained in patients with truly chemoresistant disease or early

relapse within 3 months of completion of chemotherapy. If ever these unfortunate patients are well enough they are candidates for experimental innovative treatment options.

The International Prognostic Index (IPI)

The international non-Hodgkin's lymphoma prognostic factors project derived a model of pre-treatment factors for outcome among patients treated with doxorubicin-based chemotherapy regimens [17]. Five criteria at initial presentation were found to be independent and significant poor risk factors, i.e. age >60 years, advanced stage, increased LDH, >1 extranodal site of disease, and poor performance status. These five features were used to design a model to predict an individual patient's risk of death — the International Prognostic Index.

With the introduction of the International Prognostic Index (IPI) we now have:

(1) a valid measure for comparison and understanding of different outcomes of treatment studies in patients with aggressive NHL and
(2) the possibility of a primary risk-adapted choice of initial therapy for individual patients.

Since the age limit for treatment with intensive regimens is generally set at 60 years, an age-adjusted International Index was also created for younger (<60 years) patients. Three of the previously identified risk factors — stage, performance status, and LDH level — proved to be independent significant adverse prognostic factors for this younger age group. With conventional combination chemotherapy, patients <60 years old will have a 5-year survival rate of approximately 46% if 2 of these risk factors are present, and a 5-year survival rate of approximately 32% if all 3 risk factors are present.

The IPI should now be further developed by including new biological markers of prognostic importance.

First-line high-dose chemotherapy in relation to the IPI

Several investigators have included high-dose chemotherapy programs as an integral part of the initial management of high-risk NHL patients, but risk factors were not generally assessed according to the IPI. Results of a prospective randomised trial have been reported in which the value of early high-dose chemoradiotherapy with autologous bone marrow transplantation was evaluated in patients with aggressive NHL who had slow responses to first line CHOP therapy (i.e., incomplete remissions after 3 cycles). In this trial, the outcome was not improved by high-dose treatment as compared to conventional therapy [18]. In another prospective randomised trial, high-dose chemotherapy with autologous bone marrow transplantation was compared to conventional chemotherapy as consolidation treatment in high-risk patients with intermediate grade or high grade NHL in first complete remission. High-dose consolidation failed to improve relapse free survival time and overall survival time in these patients [19]. In view of the negative results obtained in these randomised prospective studies, it is difficult to interpret the results of other non-randomised trials although outcome in some of them is favourable compared with historical controls [20–25].

Following the description of the IPI, the results of the LNH-87 trial were re-analysed according to IPI risk groups [26]. Patients in the high/intermediate (H/I) and high (H) risk groups had superior DFS and overall survival (OS) rates when treated with high-dose consolidation and autologous stem cell transplantation (ASCT) compared with those patients who received conventional dose sequential consolidation therapy (5 year actuarial DFS = 57% for high dose versus 36% for conventional dose [$p = 0.01$]; 5 year actuarial OS = 65% for high dose versus 52% for conventional dose [$p = 0.06$]). No difference in OS or DFS was observed for patients in the low (L) or low/intermediate (L/I) risk groups. These data must be interpreted cautiously, since they represent a retrospective, subset analysis from a non-stratified prospective clinical trial, but they suggest a possible role for high dose consolidation in patients with poor-risk disease.

Several randomised trials of early intensification, using high dose therapy and ASCT have now been reported for poor risk patients, and several others are in progress:

- GELA have recently reported results for the LNH-93 trial [27]. This was a randomised comparison of conventional chemotherapy using ACVB (doxorubicin, cyclophosphamide, vinblastine, bleomycin) followed by conventional dose sequential consolidation therapy, compared with an experimental intensified induction regimen (CEOP [cyclophosphamide, epirubicin, vincristine, prednisone] plus ECVBP [epirubicin, cyclophosphamide, vindesine, bleomycin, prednisone]) followed by high dose therapy and ASCT. Patients aged < 60 years, with 2 or 3 adverse risk factors according to the age-adjusted IPI were eligible. Accrual to the trial was closed after an

interim analysis. At the time of the most recent report, with a median follow up of 30 months, the 3 year EFS was 54% for the conventional arm versus 41% for the high dose arm ($p = 0.01$), and the 3 year OS was 63% for the conventional dose arm versus 47% for the high dose arm ($p = 0.003$).

- The German High Grade Lymphoma Study Group are conducting a trial comparing 3 cycles of chemotherapy using CHEOP (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) followed by high dose therapy and ASCT, with 5 cycles of CHEOP alone, for patients aged < 60, with an elevated LDH [28]. No difference in DFS or OS was reported at the first interim analysis of this trial, and a subsequent analysis using IPI risk groups shows no differences in outcome to date.
- The Italian NHL Study Group have recently completed a trial comparing VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone) alone with VACOP-B followed by high dose therapy and ASCT for *poor risk* patients (defined as bulky stage II, stages III and IV) [29]. When all patients were analysed, no difference in DFS or OS was observed. Subset analysis showed a significant improvement in DFS for IPI H/I and H risk groups receiving high dose therapy (6 year actuarial DFS = 87% for high dose compared with 48% for conventional dose therapy, $p = 0.008$). However, no difference in progression-free survival (PFS) or OS was observed.

Recent studies of *early* intensification have been notable for the relatively high rate of early disease progression in patients receiving induction therapy prior to high dose consolidation. In the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) LNH-93-3 trial, 29% of patients had progressed before reaching the high dose phase of the trial [27]. Similarly, in the German High Grade Lymphoma Study Group trial, 33% of patients failed to reach the high dose phase, mainly due to disease progression [28]. In the current UK Lymphoma Group LY02 trial, the corresponding figure is approximately 30%. Double autotransplant attempts in patients with a poor IPI have not been successful and the GELA has recently decided to stop such a pilot study after treating 39 patients.

Sequential high-dose chemotherapy

To potentially improve the efficacy of high-dose chemotherapy in the initial management of patients with aggressive NHL, Gianni and colleagues from Milan developed the concept of sequential high-dose chemotherapy. This approach is based upon the sequential administration of non-cross resistant cytotoxic drugs at near maximally tolerated doses with colony stimulating factor support in order to achieve maximal tumour kill with minimal development of drug resistance [30]. Several regimens were evaluated for feasibility, efficacy and toxicity, and a regimen consisting of five sequentially administered chemotherapy treatment phases turned out to be most suitable for clinical usage: an initial cytoreduction is the goal of phase I; high-dose cyclophosphamide is used in phase II to mobilise peripheral blood stem cells while simultaneously providing a highly active treatment for the malignant disease; high-dose methotrexate and etoposide are given during phase III and IV, respectively; and phase V is a myeloablative treatment containing melphalan and mitoxantrone. Eventually, an additional radiotherapy (phase VI) is given to patients who presented with bulky disease at diagnosis. This treatment was well tolerated, with relevant toxicities including grade III and IV myelosuppression and mucositis. Toxic deaths were encountered initially when total body irradiation (TBI) was given as part of the conditioning therapy, but fatal events could be eliminated when TBI was replaced by the myeloablative therapy described. A randomised phase III trial was then performed in which sequential high-dose treatment was compared to a control arm consisting of a third generation chemotherapy regimen (MACOP-B: methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) in newly diagnosed patients with diffuse large cell NHL and poor risk factors [31]. After a median follow-up of 43 months, treatment results were better after sequential high-dose therapy compared with MACOP-B, with a complete remission rate of 94% vs. 61%, freedom from progression in 88% vs. 41% of patients, failure-free survival in 73% vs. 40%, and overall survival in 73% vs. 62% [32].

Several groups in Europe and the US were able to confirm these results and were able to document that the sequential high-dose regimen is feasible and has an acceptable toxicity in lymphoma patients with poor prognostic features.

The results of the studies outlined above allow the following preliminary conclusions to be drawn:

1. The use of high dose therapy and ASCT in first remission (complete or partial) does not improve DFS or OS for the entire population of patients with advanced aggressive NHL.

2. Subset analysis of 2 non-stratified trials has shown a DFS and OS advantage for the high dose arm, which is restricted to patients with H/I and

H risk disease. No benefit has been observed for patients with L/I or L risk disease.

3. The use of *early* intensification, using high dose therapy and ASCT prior to the completion of full induction therapy may be inadequate, based on the results of the LNH-93-3 trial.

4. The Milan HDS protocol is the only regimen to date which has produced superior event-free survival (EFS) compared with standard dose therapy in poor risk patients in a prospective randomised trial.

The ECOG trial has demonstrated that this chemotherapy can be safely delivered in a multi-institutional trial.

Those studies in which sub-set analysis has demonstrated an advantage for high dose therapy have included the high dose regimen at the completion of full induction chemotherapy.

The encouraging data reported for the use of high-dose sequential (HDS) therapy require further comparison with standard therapy in a multi-centre context in a randomised prospective trial, compared with standard chemotherapy in patients with IPI high and high/intermediate risk disease.

The Swiss Group for Clinical Cancer Research (SAKK) therefore decided to start a multicentre international randomised phase III trial (MISTRAL) comparing the sequential high-dose strategy to standard CHOP chemotherapy. The study design is shown in Fig. 1.

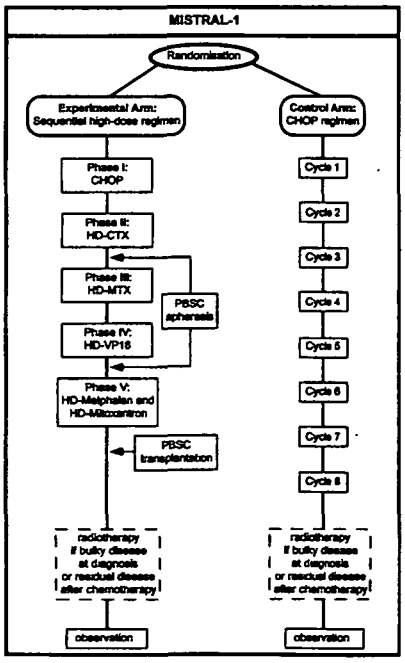

Fig. 1. MISTRAL study design (from the SAKK protocol — Swiss Group for Clinical Cancer Research — published with authorization).

Conclusion

High-dose chemotherapy is a potentially curative treatment option in chemosensitive relapsed patients with diffuse large B-cell NHL [33]. Its role in the first line treatment setting is still experimental and has to be studied in randomised trials such as the European MISTRAL study or the joint study of the Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG) and Cancer and Leukemia Group B (CALGB) in North America. We still do not know whether there is a best high dose regimen and whether there is a role for radiotherapy or purging of stem cells. The biology of diffuse large B-cell NHL must be elucidated further in order to understand the diversity of this heterogenous disease. New innovative treatment modalities are urgently needed to rescue patients with primary and secondary chemotherapy-resistant disease.

References

1 McKelvey EM, Gottlieb JA, Wilson HE, et al. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976; 38: 1484–1493.

2 Gordon LI, Harrington D, Andersen J, et al. Comparison of a second-generation combination chemotherapeutic regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. N Engl J Med 1992; 327: 1342–1349.

3 Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced Non-Hodgkin's lymphoma. N Engl J Med 1993; 328: 1002–1006.

4 Siena S, Bregni M, Brando B, Ravagnani F, Bonadonna G, Gianni AM. Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide-treated patients: Enhancement by intravenous recombinant human granulocyte-macrophage colony-stimulating factor. Blood 1989; 74: 1905–1914.

5 Gianni AM, Siena S, Bregni M, et al. Granulocyte-macrophage colony-stimulating factor to harvest circulating haemopoietic stem cells for autotransplantation. Lancet 1989; 2: 580–585.

6 Socinski MA, Cannistra SA, Elias A, Antman KH, Schnipper L, Griffin JD. Granulocyte-macrophage colony stimulating factor expands the circulating haemopoietic progenitor cell compartment in man. Lancet 1988; i: 1194–1198.

7 Stahel RA, Jost LM, Cerny T, et al. Randomized study of recombinant human granulocyte colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation for high-risk lymphoid malignancies. J Clin Oncol 1994; 12: 1931–1938.

8 Schmitz N, Linch DC, Dreger P, et al. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow trenaplsntation in lymphoma patients. Lancet 1996; 347: 353–357.

9 Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemo-

therapy in relapses of chemotherapy-sensitive non Hodgkin's lymphoma. N Engl J Med 1995; 333: 1540–1545.
10 Bosly A, Coiffier B, Gisselbrecht C, et al. Bone marrow transplantation prolongs survival after relapse in aggressive-lymphoma patients treated with the LNH-84 regimen. J Clin Oncol 1992; 10: 1615–1623.
11 Gulati S, Yahalom J, Acaba L, et al. Treatment of patients with relapsed and resistant non-Hodgkin's lymphoma using total body irradiation, etoposide, and cyclophosphamide and autologous bone marrow transplantation. J Clin Oncol 1992; 10: 936–941.
12 Kessinger A, Armitage JO, Smith DM, Landmark JD, Bierman PJ, Weisenburger DD. High-dose therapy and autologous peripheral blood stem cell transplantation for patients with lymphoma. Blood 1989; 74: 1260–1265.
13 Lazarus HM, Crilley P, Ciobanu N, et al. High-dose carmustine, etoposide and cisplatin and autologous bone marrow transplantation for relapsed and refractory lymphoma. J Clin Oncol 1992; 10: 1682–1689.
14 Vose JM, Anderson JR, Kessinger A, et al. High-dose chemotherapy and autologous hematopoietic stem-cell transplantation for aggressive non-Hodgkin's lymphoma. J Clin Oncol 1993; 11: 1846–1851.
15 Verdonck LF, Dekker AW, De Gast GC, et al. Salvage therapy with ProMACE-MOPP followed by intensive chemoradiotherapy and autologous bone marrow transplantation for patients with non-Hodgkin's lymphoma who failed to respond to first-line CHOP. J Clin Oncol 1992; 10: 1949–1954.
16 Fanin R, Ruiz de Elvira MC, Sperotto A, et al. A EBMT survey of 671 cases submitted to autologous stem cell transplantation for diffuse large B cell Lymphoma. Ann Oncol 1999; Suppl 3: 76.
17 The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987–994.
18 Verdonck LF, van Putten WLJ, Hagenbeek A, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. N Engl J Med 1995; 332: 1045–1051.
19 Haioun C, Lepage E, Gisselbrecht C, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: A study of 464 patients. J Clin Oncol 1994; 12: 2543–2551.
20 Sweetenham JW, Liberti G, Pearce R, et al. High-dose therapy and autologous bone marrow transplantation for adult patients with lymphoblastic lymphoma: Results of the European Group for Bone Marrow Transplantation. J Clin Oncol 1994; 12: 1358–1365.
21 Nademanee A, Schmidt GM, O'Donnell MR, et al. High-dose chemoradiotherapy followed by autologous bone marrow transplantation as consolidation therapy during first complete remission in adult patients with poor-risk aggressive lymphoma: A pilot study. Blood 1992; 80: 1130–1134.
22 O'Day SJ, Rabinowe SN, Neuberg D, et al. A phase II study of continuous infusion recombinant human granulocyte-macrophage colony-stimulating factor as an adjunct to autologous bone marrow transplantation for patients with non-Hodgkin's lymphoma in first remission. Blood 1994; 83: 2707–2714.
23 Gulati SC, Shank B, Black P, et al. Autologous bone marrow transplantation for patients with poor-prognosis lymphoma. J Clin Oncol 1988; 6: 1303–1313.
24 Freedman AS, Takvorian T, Neuberg D, et al. Autologous bone marrow transplantation in poor prognosis intermediate-grade and high-grade B-cell non-Hodgkin's lymphoma in first remission: A pilot study. J Clin Oncol 1993; 11: 931–936.
25 Pettengell R, Radford JA, Morgenstern GR, et al. Survival benefit from high-dose therapy with autologous blood progenitor-cell transplantation in poor-prognosis non-Hodgkin's lymphoma. J Clin Oncol 1996; 14: 586–592.
26 Haioun C, Lepage E, Gisselbrecht C, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: Updated results of the prospective study LNH87–2. J Clin Oncol 1997; 15: 1131–1137.
27 Reyes F, Lepage E, Morel P, et al. Failure of inductive high-dose chemotherapy (HDC) in poor-risk patients (PTS) with aggressive lymphoma: Updated results of the randomized LNH93–3 study. Blood 1997; 90: 594a.
28 Kaiser U, Uebelacker I, Havemann K. High dose chemotherapy with autologous stem cell transplantation in high grade NHL: first analysis of a randomized multicenter study. Bone Marrow Transpl 1998; 21: S177.
29 Santini G, Salvagno L, Leoni P, et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: Results of a prospective randomized trial by the non-Hodgkin's lymphoma Cooperative Study group. J Clin Oncol 1998; 16: 2796–2802.
30 Gianni AM, Bonadonna G. High dose chemo-radiotherapy for sensitive tumors: Is sequential better than concurrent drug delivery? Eur J Cancer Clin Oncol 1989; 25: 1027–1030.
31 Gianni AM, Bregni M, Siena S, et al. Prospective randomised comparison of MACOP-B vs. rhGM-CSF-supported high-dose sequential myeloablative chemoradiotherapy in diffuse large cell lymphomas. Proc Am Soc Clin Oncol 1991; 10: 274 (#951).
32 Gianni AM, Bregni M, Siena S, et al. High dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997; 336: 1290–1297.
33 Shipp MA, Abeloff MD, Antman KH, et al. International Consensus Conference on high-dose therapy with hematopoietic stem-cell transplantation in aggressive non-Hodgkin's Lymphomas: Report of the jury. Ann Oncol 1999; 10: 13–19.