Do we need high-dose therapy for initial treatment of high-risk Hodgkin's disease?

M. Federico, S. Luminari

Many authors have investigated the value of high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) in the treatment of patients with Hodgkin's lymphoma (HL) since the first clinical data were reported in the early 1980s. This combination is now considered an effective strategy for relapsed or refractory HL, with better results when patients are transplanted at the first event and if they are still chemosensitive to salvage chemotherapy.[1] The encouraging results obtained with high-dose salvage therapy have led to an increase in the use of HDT in patients responding to initial therapy but considered at high risk of relapse. In 1991 Carella *et al.* published a pilot study of HDT and ASCT in patients with unfavorable HL who had achieved complete remission (CR) with conventional dose chemotherapy.[2] In this study 15 patients with very poor prognosis Hodgkin's disease in remission after a treatment with MOPP/ABVD regimen, were treated with HDT and ASCT immediately after achieving CR. Thirteen patients (86.6%) remained alive in unmaintained CR at a median time of 36 months (range 10-64 months) post-transplant.

In addition to Carella's experience, Sureda *et al.* reported a promising 78% continuous CR rate after a median follow-up of 2.5 years in a group of 27 patients with poor prognosis HL. Moreau *et al.* evaluated cure rate, toxicity and late effects of early intensive therapy followed by ASCT in a group of 130 patients with advanced HL registered in the French database and transplanted in first partial remission (PR) or first CR. The 5-year overall survival rate of patients in PR and CR was 82.8% and 76.3%, respectively. Similar results were reported by Nademanee et al. and, more recently, by Sperotto *et al.*[3-6] Based on these results, and in the absence of data from comparative phase III trials, an increasing number of patients with HL were treated with HDT after the achievement of a CR. For example, the EBMT registry contains data on more than 450 patients with HL who were treated with HDT and ASCT in first CR between 1990 and 2000.

However, standard dose chemotherapy (CT) has also led to encouraging results in the treatment of patients with advanced stage HL. In addition to the good results achieved with MOPP and ABVD in the past two decades, even more promising results in terms of CR and prolonged long-term survival rates have been obtained with newer regimens such as MOPPEBVCAD and BEACOPP, even in those patients considered at high risk of failure.[7-9]

Regardless of the encouraging results reported in all these studies the question whether HDT should be included in the initial treatment plan of patients with high risk HL is still a matter of debate. Two different, randomized trials that compared conventional chemotherapy with HDT as consolidation therapy for responding patients with poor risk HL have recently been concluded and have, in our opinion, clearly demonstrated that, in patients responding to initial therapy, HDT as consolidation is not superior to consolidation with conventional chemotherapy.

The study published by Proctor *et al.*,[10] carried out on behalf of the *Scotland and Newcastle Lymphoma Group* (SNLG) compared three courses of a continuous hybrid CHT regimen plus high dose melphalan and ASCT versus five courses of the same hybrid treatment in a prospective, randomized setting in patients with poor-risk HL. One hundred and twenty-six patients were registered between 1988 and 1999, and 65 of them (52%) accepted randomization. Based on an intention-to-treat analysis, after a median follow-up of 68 months the event-free survival rate of the whole group was 78% and there was no difference between the randomization arms.

The second trial was a large co-operative study, performed by the EBMT/GISL/ANZLG/SFGM/GELA HD01 Intergroup.[11] This cooperative study was designed to verify whether patients with initial features associated with a high-risk of failure after achieving CR or PR with 4 courses of standard-dose therapy would benefit from HDT-ASCT. A total of 208 patients were registered in the study and among those 163 achieving CR or PR with 4 initial courses of ABVD or other doxorubicin-containing regimens were randomized to receive either HDT followed by ASCT (arm A) or four courses of conventional chemotherapy (Arm B). At the end of the whole treat-

From the Dipartimento di oncologia ed ematologia Università di Modena e Reggio Emilia, Centro Oncologico Modenese, Policlinico, Modena, Italy.

Correspondence: M. Federico, Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia, Centro Oncologico Modenese, Policlinico, via del Pozzo 71, Modena, Italy.

ment program, 92% of patients in Arm A and 89% in Arm B achieved a CR (p=0.6). The 5-year failure free survival was 75% in Arm A and 82% in Arm B (p=0.4). The 5-year overall survival was similar in the two treatment groups (p=1.0), being 88% in Arm A and 88% in Arm B. Finally, the 5-year relapse free survival was 88% in Arm A and 94% in Arm B: this difference was not statistically significant (p=0.3). The HD01 trial has thus demonstrated that patients with advanced, unfavorable HL, responding to front-line therapy with conventional-dose chemotherapy and then receiving intensification with HDT-ASCT had an identical outcome (in terms of CR, overall survival, RFS, and FFS rates) to those patients who received four additional courses of conventional-dose CHT.

In conclusion, given the excellent outcome of patients treated with HDT-ASCT, in the absence of a control arm in a randomized study we would probably have concluded that HDT-ASCT should be considered the treatment of choice for patients with advanced, unfavorable HL. However, the right conclusion to be drawn is different; HD01 and HD3 data definitely support the view that for patients with HL, considered at high risk according to existing prognostic scores and who respond to initial conventional chemotherapy, *more is not better* (i.e. consolidation with high dose therapy is not better than consolidation with conventional dose therapy), and most importantly, these patients should no longer be offered HDT as consolidation therapy.

The identification of patients at high risk of failure remains a key question. If there is an indication for front line use of HDT in the treatment of patients with HL, it should come from a different evaluation of prognosis in HL and, probably, from the use of different drugs or conditioning regimens. Based on currently used prognostic scores patients with high risk disease are well treated with standard chemotherapy although there probably is group of patients with poor outcome in whom the HDT option should be tested. The application of new diagnostic modalities (e.g. PET scanning and studies of tumor volume) and new serum markers with prognostic value (e.g. sCD30) and in particular their modification in the early phase of treatment could contribute to better identification of patients with high risk disease eligible for investigational therapies.

References

1. Armitage JO. Early bone marrow transplantation in Hodgkin's disease. Ann Oncol 1994;5:161-3.
2. Carella AM, Carlier P, Congiu A, Occhini D, Nati S, Santini G, et al. Autologous bone marrow transplantation as adjuvant treatment for high-risk Hodgkin's disease in first complete remission after MOPP/ABVD protocol. Bone Marrow Transplant 1991;8:99-103.
3. Sureda A, Mataix R, Hernandez-Navarro F, Jarque I, Lahuerta JJ, Tomas JF, et al. Autologous stem cell transplantation for poor prognosis Hodgkin's disease in first complete remission: a retrospective study from the Spanish GEL-TAMO cooperative group. Bone Marrow Transplant 1997;20:283-8.
4. Moreau P, Fleury J, Brice P, Colombat P, Bouabdallah R, Lioure B, et al. Early intensive therapy with autologous stem cell transplantation in advanced Hodgkin's disease: retrospective analysis of 158 cases from the French registry. Bone Marrow Transplant 1998;21:787-93.
5. Nademanee A, Molina A, Fung H, Stein A, Parker P, Planas I, et al. High-dose chemo/radiotherapy and autologous bone marrow or stem cell transplantation for poor-risk advanced-stage Hodgkin's disease during first partial or complete remission. Biol Blood Marrow Transplant 1999;5:292-8.
6. Sperotto A, Zaja F, Damiani D, et al. High-dose therapy and autologous stem cell transplantation for high-risk hodgkin's lymphoma: a single center experience. Haematologica 2001;86:1317-8.
7. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992; 327:1478-84.
8. Gobbi PG, Pieresca C, Federico M, Di Renzo N, Narni F, Iannitto E, et al. MOPP/EBV/CAD hybrid chemotherapy with or without limited radiotherapy in advanced or unfavorably presenting Hodgkin's disease: a report from the Italian Lymphoma Study Group. J Clin Oncol 1993; 11:712-9.
9. Diehl V, Sieber M, Ruffer U, et al. BEACOPP: an intensified chemotherapy regimen in advanced Hodgkin's disease. The German Hodgkin's Lymphoma Study Group. Ann Oncol 1997;8:143-8.
10. Proctor SJ, Mackie M, Dawson A, et al. A population-based study of intensive multi-agent chemotherapy with or without autotransplant for the highest risk Hodgkin's disease patients identified by the Scotland and Newcastle Lymphoma Group (SNLG) prognostic index: A Scotland and Newcastle Lymphoma Group study (SNLG HD III). Eur J Cancer 2002;38:795-806.
11. Federico M, Carella AM, Brice P. High dose therapy (HDT) and autologous stem cell transplantation (ASCT) versus conventional therapy for patients with advanced Hodgkin's disease (HD) responding to initial therapy. Proc Am Soc Clin Oncol 2002;21[abstract 1050].