



High-dose therapy and autologous stem cell transplantation vs conventional therapy for patients with advanced Hodgkin's disease responding to first-line therapy. Analysis of clinical characteristics of 51 patients enrolled in the HD01 protocol

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Whether high-dose therapy (HDT) plus autologous stem cell transplantation (ASCT) ought to be included in the initial treatment plan for those patients with unfavourable Hodgkin's disease, a wide cooperative study (HD01 protocol) was approved, comparing HDT followed by ASCT vs conventional chemotherapy (CT). Patients were eligible for the study if they had at least two of the following adverse prognostic factors: high serum LDH levels, mediastinal mass >0.45, more than one extranodal involved site, low hematocrit (<34% for women and <38% for men), and inguinal involvement. Those patients achieving complete or partial remission with four courses of ABVD or ABVD-containing chemotherapy were randomized to receive either HDT plus ASCT or four additional courses of chemotherapy, followed by ASCT in second remission, if appropriate. Between April 1993 and September 1995, 55 patients from 14 different centers have been enrolled into the trial. Twenty patients (45%) were in stage IV, and 37 patients (84%) had systemic symptoms. Twenty-seven patients (61%) had two adverse prognostic factors, and 17 patients (39%) had three or more risk factors. After four cycles of ABVD-containing CT, 44 patients were assessable for response. Overall 12 patients achieved CR (27%), 25 obtained a PR (57%) and seven patients failed to respond (16%). Thirty-six patients were randomized between ASCT (20 patients) or four additional cycles of conventional CT (16 patients). With a median follow-up after ASCT of 13 months (range 1-23 months), no major ASCT-related toxicity has been reported to the trial office. In conclusion, the first 44 patients registered in the HD01 trial and assessable for response, had a very aggressive disease and responded poorly to conventional CT, thus warranting a more aggressive approach, such as HDT followed by ASCT.

Keywords: Hodgkin's disease; autologous stem cell transplantation; therapy

Introduction

Combination chemotherapy is the treatment of choice of patients with advanced Hodgkin's disease (HD).^{1,2} A variety of regimens, including ABVD, MOPP/ABVD, MOPP/EBV/CAD hybrid, and Stanford V all induce high-remission rates,³⁻⁶ but more than one third of remitters usually relapse. Patients who relapse early after chemotherapy require additional therapy, but only a few cases can be cured with appropriate salvage therapy, and the prognosis remains poor.⁷ Considering the unsatisfactory results obtained with conventional salvage therapy, in recent years an increasing interest in the opportunity of consolidating the first complete remission in high-risk patients with additional treatments has emerged.⁸

High-dose therapy followed by stem cell transplantation (ASCT) is an effective procedure for advanced HD.⁹⁻¹¹ However, results are better when patients are transplanted earlier in the course of the disease.¹²

In 1991, Carella *et al*¹³ published a pilot study of aggressive chemotherapy followed by ASCT in patients with very unfav-

orable HD achieving complete remission with first-line therapy. In a recent update of this experience the results continue to be very promising, with a 87% long-term survival rate.¹⁴

Despite these promising results, the inclusion of high-dose therapy (HDT) plus ASCT in the initial treatment plan for those patients with unfavorable HD is still a matter of debate. A key question is the recognition of patients at high risk of relapse. A number of characteristics have been associated with unfavorable rates of remission, duration of remission, and overall survival in patients with advanced-stage disease.¹⁵⁻¹⁷ These include systemic symptoms, age greater than 40 years, mediastinal bulky disease, multiple extranodal sites of involvement, anemia, low albumin levels, and high serum lactate dehydrogenase (LDH). Recently Straus *et al*⁸ found that the major factors negatively affecting the duration of complete remission in patients with advanced HD were high serum LDH, age more than 45 years, mediastinal mass greater than 0.45 of the thoracic diameter, two or more extranodal sites, inguinal node involvement and low hematocrit. Patients with two or more unfavorable characteristics were much more likely to fail treatment than those with none or only one unfavorable factor.

In April 1993, in an attempt to improve the curability of HD and reduce the risk of relapse after initial response, we started a wide cooperative study (HD01 protocol) comparing HDT followed by ASCT vs conventional chemotherapy (CT) for patients with unfavorable HD according to Straus criteria, responding to first-line therapy.

We now report the preliminary results of this ongoing trial, including the analysis of clinical characteristics and the response to initial therapy of patients enrolled in the first 2 years.

Methods

Between April 1993 and September 1995, 55 patients with histologically confirmed HD were registered at the trial office. Previously untreated patients from 15 to 60 years of age were eligible if they had at least two Straus' adverse prognostic factors. Additional criteria for inclusion into the study were: ECOG performance status 0-2; good marrow recovery; normal renal and hepatic function (unless directly attributable to lymphoma); normal cardiac and pulmonary functions. Patients must be psychologically capable of undergoing bone marrow transplant and its attendant period of strict isolation.

Exclusion criteria included: severe or symptomatic restrictive or obstructive lung disease (or a DLCO less than 60% of predicted); ejection fraction less than 50%, signs or symptoms of congestive heart failure, or myocardial infarction within the past 3 months, angina pectoris, any major ventricular arrhythmia, or uncontrolled blood pressure; insulin-dependent diabetes mellitus; active infections; concurrent or previous malignancies (other than non-melanomatous skin cancer), surgically cured carcinoma *in situ* of the cervix, or a history of cancer that had not been active in the past 5 years; HIV infection.

Response to treatment had to be assessed at least 4 weeks after the end of chemotherapy. This allowed randomization to occur at the same time for all induction regimens.

To assess the response to the initial chemotherapy, all tests that had abnormal results on staging before therapy were repeated. Complete remission (CR) was defined as the complete disappearance of all previously detectable disease. Partial remission (PR) was defined as a reduction by at least 50% in the sums of the products of the biperpendicular diameters of all measurable masses. No response (NR) was defined as less than 50% reduction in the sums of the products of the biperpendicular diameters of all measurable tumor masses, or stable disease or any increase in size of previously documented disease, or the appearance of disease at any sites.

Those patients achieving complete or partial remission with four courses of ABVD or ABVD-containing chemotherapy were asked to enter the trial, thus were randomized to receive either HDT plus ASCT or four additional courses of chemotherapy, followed by ASCT in second remission, if appropriate.

Sample size determination

In the present study we estimated a success rate of 45% (in terms of 5-year failure-free survival) for patients treated with chemotherapy alone and a success rate of 70% for patients treated with chemotherapy plus ASCT. Assuming a larger minus smaller success rate of 25% between the two arms, a power of 90% and a level of significance of 0.05, and using a one-sided test, we planned an accrual of 73 patients in each arm.¹⁹ Statistical analyses were performed by the Statistics and Data Management unit of Division of Medical Oncology, University of Modena. It was the responsibility of the clinical investigator to ensure that all clinical record forms designed for the study were completed satisfactorily and returned to the trials office.

Results

At the time of present analysis, 11 patients were still under induction therapy and not assessable for response. For the remaining 44 patients both registration and induction forms were available. The clinical characteristics of all these 44 patients are summarized in Table 1. Twenty patients (45%) were in stage IV, and 37 patients (84%) had systemic symptoms. Twenty-seven patients (61%) had two adverse prognostic factors, and 17 patients (39%) had three or more risk factors.

Large mass, low hematocrit values and high serum LDH levels were the most frequent adverse prognostic factors present at time of diagnosis.

After four courses of ABVD or ABVD-containing regimens, 12 patients achieved a CR and 25 patients had had a PR. Four patients failed to respond and three patients interrupted the planned therapy for major toxicity. However, one patient in PR after induction therapy refused randomization and went off study. Finally, 36 patients (12 in CR and 24 in PR) were randomized. Twenty patients underwent ASCT and 16 continued with four additional courses of standard chemotherapy.

With a median follow-up after ASCT of 13 months (range 1–23 months), no major ASCT-related toxicity has been reported to the trial office.

Table 1 Clinical characteristics of patients enrolled into HD01 protocol

Characteristic	No. of patients (%)
Patients	
Registered	55
Assessable	44
Sex	
Male	22 (50)
Female	22 (50)
Age, years	
Mean	32
Range	15–60
Stage	
II	15 (34)
III	9 (20)
IV	20 (46)
Systemic symptoms	37 (84)
Large mass	29 (66)
>1 extranodal site	9 (20)
Inguinal involvement	19(43)
Low hematocrit ^a	29(66)
High serum LDH ^b	24/42 (57)

^a<38% for males and <34% for females.

^bAbove the upper limit of the normal range.

Conclusions

This ongoing cooperative study would definitely assess, with a prospective randomized trial, the value of a policy of high-dose, myeloablative therapy followed by autologous stem cell transplantation in patients with advanced, unfavorable Hodgkin's disease responding to first-line therapy with ABVD or ABVD containing regimens.

A very important first step toward this question is the identification of patients with unfavorable Hodgkin's disease. Applying the Straus criteria for definition of unfavorable disease,¹⁸ in a previous study we had found that patients with two or more adverse prognostic factors and treated with standard-dose therapy had a 57 month disease-free survival rate of 53%, confirming that a subset of patients with a poor prognosis can be identified.²⁰ The preliminary results of the present trial continue to support our previous impression: the very low (29%) CR rate achieved in patients enrolled in the HD01 protocol (and treated by expert hematologists in referenced centers) after four courses of chemotherapy allows us to consider the Straus criteria as clinically appealing and able to identify patients at high risk of treatment failure.

On the basis of the present data, we believe that the decision to study the advantages of an earlier use of high-dose therapy plus ASCT in these patients appears once more appropriate.

A second important question is the safety of high-dose therapy plus ASCT. Two to 10% of deaths due to ABMT or ASCT toxicity can be expected. To date in the present study no deaths have occurred. Although more patients have to be enrolled and a longer follow-up is crucial, the absence of ASCT-related deaths among the first 20 transplanted patients encourage the prosecution of the trial and confirm the increasing safety of high-dose therapy if performed in the initial course of the disease.

In conclusion, if we continue to include in the HD01 study exclusively patients with very aggressive HD, and if we accrue the planned number of patients, we will probably answer the question as to the role of high-dose therapy in the initial treatment of patients with unfavorable HD.

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Appendix

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