# High-Dose Therapy and Autologous Stem-Cell Transplantation Versus Conventional Therapy for Patients With Advanced Hodgkin's Lymphoma Responding to Front-Line Therapy

By Massimo Federico, Monica Bellei, Pauline Brice, Maura Brugiatelli, Arnon Nagler, Christian Gisselbrecht, Luciano Moretti, Philippe Colombat, Stefano Luminari, Francesco Fabbiano, Nicola Di Renzo, Anthony Goldstone, and Angelo Michele Carella for the EBMT/GISL/ANZLG/SFGM/GELA Intergroup HD01 Trial

***Purpose:*** **To determine whether high-dose therapy (HDT) with autologous stem-cell transplantation (ASCT) should be included in the initial consolidative treatment of patients with advanced, unfavorable Hodgkin's lymphoma (HL).**

***Patients and Methods:*** **One hundred sixty-three patients achieving complete remission (CR) or partial remission (PR) with four initial courses of doxorubicin, bleomycin, vinblastine, and dacarbazine, or other doxorubicin-containing regimens, were randomly assigned to receive HDT plus ASCT (83 patients) versus four courses of conventional chemotherapy (80 patients). Unfavorable HL was defined as the presence of at least two of the following poor prognostic factors: high lactate dehydrogenase level, large mediastinal mass (greater than at least 33% of the thoracic diameter), more than one extranodal site, low hematocrit level, and inguinal involvement.**

***Results:*** **At the end of the treatment program, 92% of patients in arm A and 89% in arm B achieved a CR ($P = .6$). After a median follow-up of 48 months, the 5-year failure-free survival rates were 75% (95% confidence interval [CI], 65 to 85) in arm A and 82% (95% CI, 73 to 90) in arm B ($P = .4$). The 5-year overall survival rates were 88% (95% CI, 80 to 96) in arm A and 88% (95% CI, 79 to 96) in arm B ($P = .99$). The 5-year relapse-free survival rates were 88% in arm A (95% CI, 80 to 96) and 94% in arm B (95% CI, 88 to 100), and the difference was not significant ($P = .3$).**

***Conclusion:*** **Patients with advanced unfavorable HL achieving CR or PR after four courses of doxorubicin-containing regimens have a favorable outcome with conventional chemotherapy. No benefit from an early intensification with HDT and ASCT was shown.**

***J Clin Oncol 21:2320-2325.*** 

THERE IS general agreement that combination chemotherapy (CHT) is the treatment of choice for patients with advanced Hodgkin's lymphoma (HL).[1,2] A variety of regimens, including ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine),[3] alternating MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)/ABVD,[4] and MOPP/ABV (doxorubicin, bleomycin, and vinblastine) hybrid,[5] induce high levels of complete remission (CR) and prolong long-term survival rates. However, 5% to 10% of patients fail to obtain a CR and up to 30% of responders usually relapse and require additional therapy.[6] Moreover, less than one third of patients who relapse early after CHT can be rescued with appropriate salvage therapy.[6,7]

High-dose therapy (HDT) followed by autologous stem-cell transplantation (ASCT) is an effective procedure for relapsed or refractory HL, with better results when patients undergo transplantation at the first event and if they are still chemosensitive to salvage CHT.[8,9] The encouraging results with high-dose salvage therapy have raised the question of whether it is appropriate to consider HDT as consolidation therapy in first remission in the subset of patients at high-risk of relapse. In 1991, Carella et al[10] published a pilot study of HDT and ASCT in patients with unfavorable HL who had achieved CR with conventional-dose CHT. Despite these promising results, the inclusion of HDT plus ASCT in the initial treatment plan for patients with unfavorable HL was a matter of debate in the early 1990s. A key question was the recognition of patients at high risk of failure. A number of characteristics have been associated with unfavorable outcome and include systemic symptoms, older age, mediastinal bulky disease, multiple extranodal sites of involvement, anemia, low albumin levels, and high serum lactate dehydrogenase (LDH) levels.[11-13] Straus et al[14] found that the major factors negatively affecting the duration of CR in patients with advanced HL were high serum LDH, age older than 45 years, a large

*From the Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia, Modena; Divisione di Ematologia, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo; Divisione di Ematologia, Azienda Ospedaliera Papardo, Messina; Divisione di Ematologia, Centro Trapianti Midollo Osseo USL 3, Pesaro; Divisione di Ematologia, Ospedale Cervello, Palermo; Servizio di Oncologia Medica ed Ematologia, Ospedale Oncologico Regionale, Rionero in Vulture, Italy; Institut d'Hematologie, Hopital Saint-Louis, Paris; Service D' Oncologie Medicale et des Maladies des Sang, Unitè de Greffe de Moelle Osseuse, Centre Hopital Bretonneau, Tours Cedex, France; Bone Marrow Transplant Department, Chaim Sheba Medical Center, Tel-Hashemer, Israel; and Department of Haematology, University College London, London, United Kingdom.*

*Submitted November 20, 2002; accepted April 1, 2003.*

*Supported by grants from "Associazione Angela Serra per la Ricerca sul Cancro," Modena, Consiglio Nazionale delle Ricerche (no. 92.02122.PF 39), Roma, and "Associazione Italiana per la Ricerca sul Cancro" (1993), Milano, Italy.*

*Massimo Federico and Angelo Michele Carella contributed equally to this study.*

*Address reprint requests to Massimo Federico, MD, Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia, Centro Oncologico Modenese, via del Pozzo, 71 41100 Modena, Italy; email: federico@unimore.it.*



*0732-183X/03/2112-2320/$20.00*


DOI: 10.1200/JCO.2003.11.103

mediastinal mass, two or more extranodal sites, inguinal node involvement, and low hematocrit. In an attempt to improve the cure rate of advanced, unfavorable HL and to reduce the risk of relapse after initial response, in April 1993 we started a large cooperative study comparing HDT followed by ASCT versus conventional CHT in patients with unfavorable HL in CR or in partial remission (PR) after four courses of ABVD or other doxorubicin-containing regimens. Because at the time this study was conceived the International Hodgkin's Disease Prognostic Factor (IHDPF) index[15] was not yet published, we decided to identify patients at high-risk using a Straus-derived system. We present the final results of this trial, closed in December 2000 with the randomization of 163 patients.

## PATIENTS AND METHODS

Previously untreated patients aged 15 to 60 years were eligible if they had, in addition to advanced stage, at least two of the following adverse prognostic factors: elevated serum LDH levels, large mediastinal mass (greater than at least 33% of the thoracic diameter measured at T5/T6 level on chest radiographs), stage IV with more than one extranodal site of disease, low hematocrit ($\leq$ 34% for women and $\leq$ 38% for men), and inguinal involvement. Moreover, patients registered at the Groupe d'Etudes des Lymphoma de l'Adulte (GELA) trial office were eligible in the presence of at least three adverse prognostic factors of six (the same five parameters mentioned above plus bone marrow involvement).

Patients had to have an Eastern Cooperative Oncology Group performance status of 0 to 2 and be able to undergo bone marrow transplantation. Prestudy investigations included an accurate medical history and physical examination, full blood count and differential, serum biochemistry profile, chest x-ray, chest and abdomen computed tomography, bone marrow aspirate, and trephine biopsy. Additional examinations necessary to document lesions in any site were used as clinically indicated. Complete restaging of evaluable sites in each patient was performed at the end of the first four courses of CHT and after the end of the therapy assigned by randomization.

CR was defined as the complete disappearance of all previously detectable disease; unconfirmed CR was used in case of persisting stable residual masses without evidence of disease. PR was defined as a reduction by at least 50% in the sum of the products of the biperpendicular diameters of all measurable masses without clinical or biologic symptoms. No response was defined as less than 50% reduction of tumor masses or as stable disease or progression at any site.

Registration and randomization were performed separately at the trial offices of the Gruppo Italiano Studio Linfomi (GISL), the GELA, and the Australian & New Zealand Lymphoma Group (ANZLG). The protocol was approved by the local ethical committees of each center. All patients gave their informed consent at registration, despite the fact that some later withdrew this consent.

### *Treatment Protocol*

Among the 163 randomly assigned patients, 75 received ABVD, 23 alternated MOPP/ABVD, and 62 MOPP/ABV hybrid; three were treated with different regimens (CVPP/ABV, 2; OPP/ABVD, 1). Patients achieving CR or PR with four courses of CHT were randomly assigned to receive either HDT-ASCT or four additional courses of the same CHT used in the induction phase. Stem-cell harvesting and cryopreservation were performed as soon as possible after hematologic recovery from the last course of induction CHT. The median time between the administration of the fourth course of CHT and stem-cell harvest was 54 days (range, 6-189). In 45 of the 70 patients who actually underwent transplantation, the source of stem cells was peripheral blood; in the other 25 cases, the source was bone marrow. The HDT administered before the reinfusion of autologous stem cells consisted of BEAM (carmustine, etoposide, cytarabine, and melphalan)[8] in 60 cases and CVB (cyclophosphamide, carmustine, and etoposide)[16] in the remaining 10 patients. After ASCT, recombinant human granulocyte colony-stimulating factor was administered until neutrophil recovery.

Involved-field radiotherapy (RT) was planned for patients with initial bulky disease or with residual masses. No specific criteria for definition of residual masses were provided, allowing the decision to be at physician's discretion.

### *Statistical Analysis*

In the present study, we estimated 5-year failure-free survival (FFS) rates of 45% for patients treated with CHT alone and 70% for patients treated with HDT-ASCT. With a power of 90% and a level of significance of .05, using a one-sided test, 73 patients had to be assigned to each treatment arm.[17] Moreover, considering a dropout rate of 10% of patients, a final accrual of 160 patients was planned.

HDT-ASCT efficacy, compared with the policy of four courses of CHT, was first assessed in terms of the percentage of CR rate, overall survival, relapse-free survival (RFS), and FFS.

Differences in CR rate between the groups were analyzed by the Pearson's $\chi^2$ test for contingency tables. Overall survival, RFS, and FFS curves were estimated by the method of Kaplan-Meier. Overall survival was calculated from the beginning of treatment until death from any cause or until date of last contact for living patients. In patients in CR, RFS was calculated from the end of induction therapy to the first evidence of disease relapse. FFS was measured from the date of randomization to failure, defined as either no achievement of CR at the end of therapy, or relapse after a CR, or death from any cause. *A P* value of .05 (two-sided) was considered the limit of significance for each analysis

Interim analyses were performed twice during the study. After a detailed analysis of available data, in both circumstances the trial data monitoring committee agreed to continue and complete the trial.

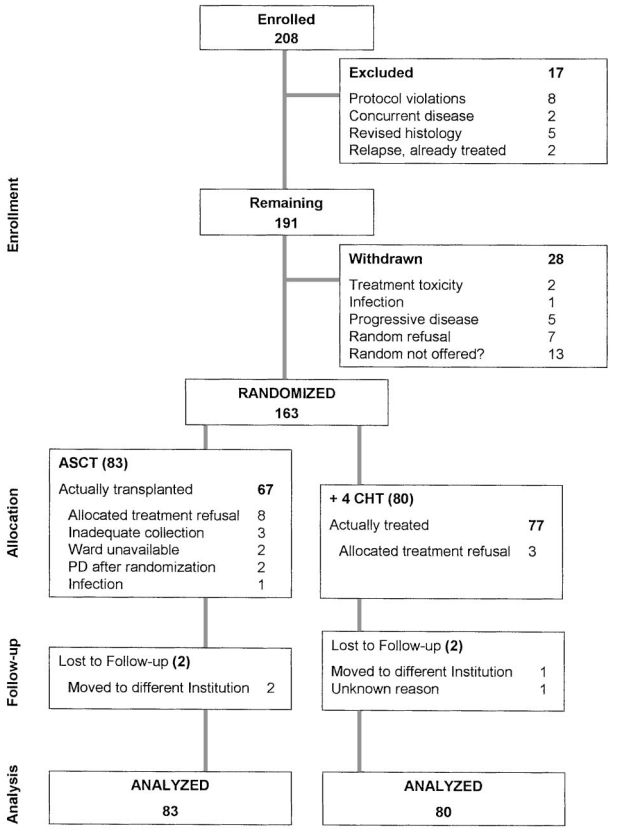


**Fig 1. Flow diagram of the HD01 trial. ASCT, autologous stem-cell transplantation; CHT, chemotherapy; PD, progressive disease.**

**Table 1. Characteristics of 163 Randomly Assigned Patients**

| Characteristic | Treatment | | | | |
|---|---|---|---|---|---|
| | Arm A (n = 83) | | Arm B (n = 80) | | |
| | No. of Cases | % | No. of Cases | % | *P* |
| Age, years | | | | | .99 |
| Median | 31 | | 32 | | |
| Range | 15-61 | | 15-58 | | |
| Male sex | 42 | 51 | 38 | 48 | .7 |
| Ann Arbor stage IV | 53 | 64 | 47 | 59 | .5 |
| Systemic symptoms | 76 | 92 | 70 | 88 | .4 |
| Bulky disease | 59 | 71 | 54 | 68 | .7 |
| > 1 Extranodal site | 41 | 49 | 39 | 49 | .99 |
| Elevated LDH | 53 | 64 | 49 | 61 | .7 |
| Inguinal involvement | 42 | 51 | 38 | 48 | .7 |
| Low hematocrit | 61 | 74 | 60 | 75 | .9 |
| Straus index | | | | | .7 |
| 2-3 | 58 | 70 | 53 | 66 | |
| ≥4 | 25 | 30 | 27 | 34 | |
| IHDPF index ≥3 (133 pts) | 47 | 68 | 37 | 58 | .3 |
| Follow-up, months | | | | | |
| Median | 49 | | 48 | | |
| Range | 6-102 | | 9-99 | | |
| CR rate after induction CHT | 32 | 39 | 36 | 45 | .4 |
| Induction treatment | | | | | .3 |
| ABVD | 37 | 45 | 38 | 48 | |
| MOPP/ABVD | 8 | 10 | 15 | 19 | |
| MOPP/ABV hybrid | 36 | 43 | 26 | 32 | |
| CVPP/ABV | 1 | 1 | 1 | 1 | |
| OPP/ABVD | 1 | 1 | | | |

Abbreviations: LDH, lactate dehydrogenase; IHDPF, International Hodgkin's Disease Prognostic Factor; CR, complete remission; CHT, chemotherapy; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; MOPP/ABV, doxorubicin, bleomycin, and vinblastine; CVPP, cyclophosphamide, vincristine, procarbazine, and prednisone; OPP, vincristine, procarbazine, and prednisone.

Only four patients were lost to follow-up after 23, 32, 32, and 42 months, respectively. At the time of the present analysis, the median follow-up from the date of registration for patients still living was 48 months (range, 9-102).

## RESULTS

Between April 1993 and December 2000, 208 participants were registered in the study. The flow of all participants through each phase of the study is reported in Figure 1. After registration, 17 patients were excluded by the trial office for the following reasons: major protocol violations (eight patients), diagnosis of non-HL after centralized histologic revision (five patients), relapse after previous treatment with radiotherapy (two patients), and presence of concurrent disease not allowing the delivery of full doses of drugs (two patients).

Among 191 eligible patients, 163 were randomly assigned and 28 were not. Reasons for withdrawal from the trial before randomization were as follows: refusal to be randomly assigned (seven patients), progressive disease (five patients), treatment toxicity (two patients), and infection (one patient); moreover, 13 patients were not randomly assigned because it was not requested by the physician.

The clinical characteristics of the 163 randomly assigned patients are summarized in Table 1. The median age was 31 years (range, 15-61). The HDT and conventional CHT groups were similar with respect to all the prognostic variables used for selecting patients. At randomization, the two groups were fully balanced in terms of response to the first four courses of CHT (Table 1).

The primary analysis was in terms of intention to treat. However, in the group of 83 patients allocated to the HDT-ASCT arm (arm A), 67 actually underwent transplantation and 16 did not for the following reasons: refusal of allocated treatment (eight patients), inadequate collection of progenitor cells (three patients), ward unavailable (two patients), progression of the disease before admission to HDT (two patients), and severe infection (one patient). In the group of 80 patients allocated to CHT (arm B), 77 completed the planned therapy and three refused the allocated treatment and underwent HDT-ASCT.

Sixty-eight patients (82%) assigned to arm A achieved CR, compared with 60 (75%) assigned to arm B. The difference was not significant ($P = .3$). After postinduction therapy, 44 (53%) patients in arm A and 45 (56%) patients in arm B were treated with 36 to 40 Gy of involved-field RT.

At the end of the treatment program, 76 (92%) patients in arm A and 71 (89%) patients in arm B achieved CR, and no significant difference between the two treatment arms was found ($P = .6$).

To date 17 deaths have occurred: eight in arm A (disease progression, four; treatment toxicity, one; infection, one; heart

attack, one; second cancer, one) and nine in arm B (disease progression, eight; second cancer, one). The toxic death recorded in arm A was caused by pulmonary venous occlusive disease, 5 months after ASCT. The 5-year survival rates were 88% (95% confidence interval [CI], 80 to 96) for patients randomly assigned to arm A and 88% (95% CI, 79 to 96) for patients assigned to arm B (Fig 2A). Eight patients in arm A and four in arm B relapsed 2 to 96 (median, 39) months after the achievement of CR. Similarly, the 5-year RFS rates were 88% (95% CI, 80 to 96) and 94% (95% CI, 88 to 100) for patients assigned to arms A and B, respectively ($P = .3$). Overall, after a median follow-up of 48 months, 19 treatment failures in arm A and 14 in arm B were recorded ($P = .4$).

The 5-year FFS rates were 75% (95% CI, 65 to 85) for patients randomly assigned to arm A and 82% (95% CI, 73 to 90) for patients assigned to arm B (Fig 2B) ($P = .4$). The results were similar in the 95 patients in PR at the time of randomization. The 5-year survival rates were 86% (95% CI, 76 to 96) for 51 patients randomly assigned to HDT-ASCT compared with 88% (95% CI, 77 to 99) for 44 patients assigned to CHT ($P = .6$). The 5-year RFS rates were 81% (95% CI, 69 to 93) and 92% (95% CI, 83 to 100) for patients assigned to arms A and B, respectively ($P = .2$). Finally, the 5-year FFS rates were 66% (95% CI, 52 to 80) for patients randomly assigned to HDT-ASCT and 77% (95% CI, 64 to 89) for patients assigned to CHT. Once again, the difference was not significant ($P = .4$).

An additional analysis was performed in the group of 84 patients with three or more risk factors according to the IHDPF index.[15] At the end of the planned therapy, 43 patients (91%) in arm A and 31 (84%) in arm B achieved CR, without any difference between the two treatment arms ($P = .3$). In this subset of patients, no difference was found in terms of 5-year overall survival ($P = .5$), RFS ($P = .6$), or FFS ($P = 0.99$).

Analyses according to actual treatment received did not change the results. No differences emerged between the two treatment groups in terms of complete response (93% and 89% in arms A and B, respectively, $P = .6$), 5-year overall survival rates (90% and 87%, $P = .9$), 5-year RFS rates (89% and 94%, $P = .3$), and 5-year FFS rates (76% and 83%, $P = .5$). No difference at all was observed when the analysis was restricted to patients in PR after induction treatment or in patients with IHDPF score greater or equal to 3 (data not shown).

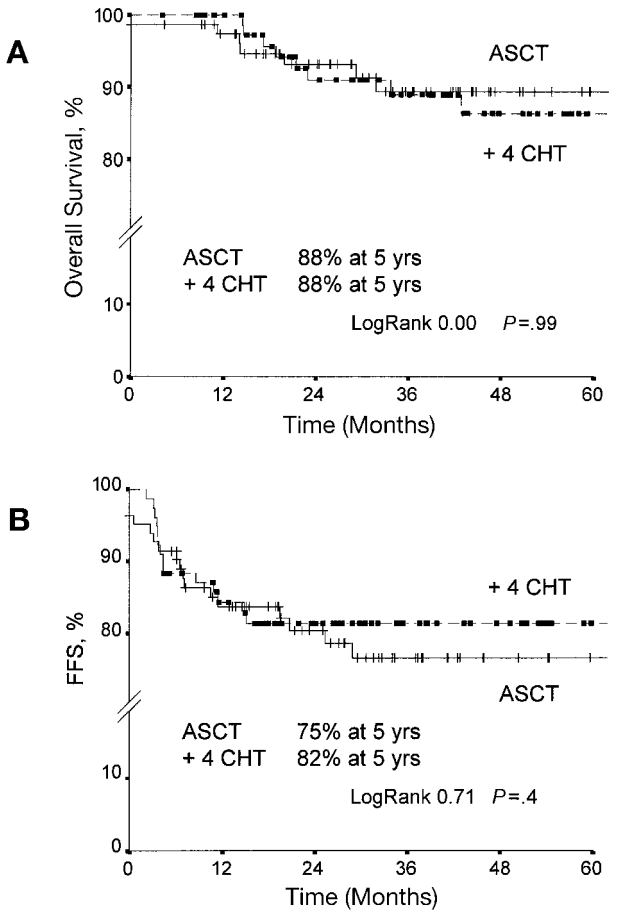


**Fig 2. (A) Overall survival and (B) failure-free survival (FFS) of all 163 randomized patients. ASCT, Autologous stem-cell transplantation; CHT, chemotherapy.**

## DISCUSSION

This cooperative study was designed with the aim of verifying whether patients with initial features associated with high-risk of failure after achieving CR or PR with four courses of standard-dose therapy would benefit from HDT-ASCT. Our study has demonstrated that patients with advanced unfavorable HL according to the high-risk assumed features, who responded to front-line therapy with conventional-dose CHT and received an intensification with HDT-ASCT, had an identical outcome as those who received four additional courses of conventional-dose CHT in terms of CR, overall survival, RFS, and FFS rates of patients.

These apparently unexpected results were determined by the excellent outcome of patients randomly assigned to the postinduction treatment with conventional-dose CHT. In fact, although the group of patients randomly assigned to HDT-ASCT had the outcome that was expected when the trial was designed, surprisingly the control group had an even more favorable outcome, by far higher than the predicted 45% 5-year FFS rate. Possible explanations for the good results observed in the control arm could be the selection of randomly assigned patients on the basis of response to the first four courses of treatment and additional RT in approximately 50% of patients. Chemosensitivity has always been a major factor for a good outcome in patients with HL, and this favorable factor may circumvent the high-risk factors selected at diagnosis.[14]

Recently Carde et al evaluated the influence of early response to CHT on patients enrolled in the 20884 trial of the European Organization for Research and Treatment of Cancer (EORTC),[18] the MDH82 trial of the French Society of Pediatric Oncology,[19] and the HD9 trial of the German Hodgkin's Lymphoma Study Group,[20] showing that in patients with advanced HL an early response to CHT is an important surrogate for final outcome.[21] The lessons from the European Organization for Research and Treatment of Cancer 20884 and the MDH82 and HD9 trials,

combined with the results of our prospective randomized study, should be kept in mind in future treatment decisions. Given the excellent outcome of patients treated with HDT-ASCT, in the absence of a control arm through a randomized study, we would probably have concluded that HDT-ASCT would be considered the treatment of choice for patients with advanced, unfavorable HL.

Our data definitely support the view that for patients responding to initial conventional CHT, " more is not better" (ie, consolidation with HDT is not better than consolidation with conventional-dose therapy), and most importantly, HDT as consolidation therapy should no longer be offered to these patients.

Results similar to ours have recently been published by Proctor et al on behalf of the Scotland and Newcastle Lymphoma Group. In their Scotland and Newcastle Lymphoma Group HD3 study they compared, in a prospective randomized trial, three courses of a continuous hybrid CHT regimen plus high-dose melphalan and ASCT versus five courses of the same hybrid treatment in poor-risk HL. One hundred twenty-six patients were registered between 1988 and 1999, and 65 (52%) patients 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.[22]

To date there are only a few published reports dealing with the retrospective analysis of patients treated with HDT as part of the primary treatment. In addition to Carella's experience,[10] Sureda et al[23] reported a promising 78% continuous CR after a median follow-up of 2.5 years in a group of 27 patients with poor-prognosis HL. Moreau et al[24] 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 who underwent transplantation in first PR or first CR. In this study, the 5-year overall survival rates of patients in PR and CR were 82.8% and 76.3%, respectively. Similar results have been reported by Nademanee et al[25] and, more recently, by Sperotto et al.[26]

When we planned the HD01 protocol, a crucial issue was the identification of patients with unfavorable HL. At that time, the IHDPF index was not yet available. However, a number of characteristics had been associated with unfavorable remission rates, remission duration, and overall survival in patients with advanced-stage disease. These included systemic symptoms, age older than 40 years, large mediastinal mass, multiple extranodal sites, low hematocrit, high serum LDH level, and elevated erythrocyte sedimentation rate. On the basis of published data, in 1993 we judged that patients with advanced stage and two or more of the prognostic factors (excluding age) proposed by Straus,[14] could be considered at high-risk of failure and suitable for testing the usefulness of up-front HDT.

Another relevant issue of our study was the evaluation of safety of an early use of HDT followed by ASCT. According to published data, 2% of deaths caused by ABMT or ASCT toxicity can be expected.[27] In the present study, only one toxic death occurred, thus confirming the increasing safety of this procedure when performed in the initial course of the disease, although no data are possible concerning the long-term toxicity expected in 10 years or more (eg, fertility, second neoplasm, cardiac toxicity).

Based on the results of the present trial we can definitely conclude that patients with advanced, unfavorable HL who are in CR or PR after four courses of front-line conventional-dose CHT do not benefit from an early intensification with HDT and ASCT, but should be treated with four additional courses of the same therapy used in the induction phase.

## APPENDIX

The appendix is available online at www.jco.org.

## REFERENCES

1. 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 327:1478-1484, 1992

2. De Vita VT Jr, Hubbard SM, Longo DL: The chemotherapy of lymphomas: Looking back, moving forward—The Richard and Hinda Rosenthal Foundation award lecture. Cancer Res 47:5810-5824, 1987

3. Bonadonna G, Zucali R, Monfardini S, et al: Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 36:252-259, 1975

4. Bonadonna G, Valagussa P, Santoro A: Alternating non-cross-resistant combination chemotherapy or MOPP in stage IV Hodgkin's disease: A report of 8-year results. Ann Intern Med 104:739-746, 1986

5. Klimo P, Connors JM: MOPP/ABV hybrid program: Combination chemotherapy based on early introduction of seven effective drugs for advanced Hodgkin's disease. J Clin Oncol 3:1174-1182, 1985

6. Lohri A, Barnett M, Fairey RN, et al: Outcome of treatment of first relapse of Hodgkin' s disease after primary chemotherapy: Identification of risk factors from the British Columbia experience 1970 to 1988. Blood 77:2292-2298, 1991

7. Urba WJ, Longo DL: Hodgkin's disease. N Engl J Med 326:678-687, 1992

8. Gribben JG, Linch DC, Singer CR, et al: Successful treatment of refractory Hodgkin's disease by high-dose combination chemotherapy and autologous bone marrow transplantation. Blood 73:340-344, 1989

9. Armitage JO: Early bone marrow transplantation in Hodgkin's disease. Ann Oncol 5:161-163, 1994

10. Carella AM, Carlier P, Congiu A, 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 8:99-103, 1991

11. Gobbi PG, Cavalli C, Federico M, et al: Hodgkin's disease prognosis: A directly predictive equation. Lancet 1:675-679, 1988

12. Carde P, MacKintosh FR, Rosenberg SA: A dose and time response analysis of the treatment of Hodgkin's disease with MOPP chemotherapy. J Clin Oncol 1:146-153, 1983

13. Proctor SJ, Taylor P, Donnan P, et al: A numerical prognostic index for clinical use in identification of poor-risk patients with Hodgkin' s disease at diagnosis. Scotland and Newcastle Lymphoma Group (SNLG) Therapy Working Party. Eur J Cancer 27:624-629, 1991

14. Straus DJ, Gaynor JJ, Myers J, et al: Prognostic factors among 185 adults with newly diagnosed advanced Hodgkin's disease treated with alternating potentially noncross-resistant chemotherapy and intermediate-dose radiation therapy. J Clin Oncol 8:1173-1186, 1990

15. Hasenclever D, Diehl V: A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 339:1506-1514, 1998

16. Jagannath S, Dicke KA, Armitage JO, et al: High-dose cyclophosphamide, carmustine, and etoposide and autologous bone marrow transplantation for relapsed Hodgkin' s disease. Ann Intern Med 104:163-168, 1986

17. Simon R: Design and conduct of clinical trials, in De Vita V, Hellman S, Rosenberg S (eds): Cancer, Principles and Practice of Oncology. Philadelphia, Lippincott, 1989

18. Raemaekers J, Burgers M, Henry-Amar M, et al: Patients with stage III/IV Hodgkin's disease in partial remission after MOPP/ABV chemotherapy have excellent prognosis after additional involved-field radiotherapy: Interim results from the ongoing EORTC-LCG and GPMC phase III trial. The EORTC Lymphoma Cooperative Group and Groupe Pierre-et-Marie-Curie. Ann Oncol 8:111-114, 1997

19. Landman-Parker J, Pacquement H, Leblanc T, et al: Localized childhood Hodgkin' s disease: Response-adapted chemotherapy with etoposide, bleomycin, vinblastine, and prednisone before low-dose radiation therapy: Results of the French Society of Pediatric Oncology Study MDH90. J Clin Oncol 18:1500-1507, 2000

20. 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 8:143-148, 1997

21. Carde P, Koscielny S, Franklin J, et al: Early response to chemotherapy: A surrogate for final outcome of Hodgkin' s disease patients that should influence initial treatment length and intensity? Ann Oncol 13:86-91, 2002

22. Proctor SJ, Taylor PRA, Mackie M, et al: SNLG HD3 study: A randomized trial comparing 3 courses of continuous hybrid treatment in poor-risk Hodgkin' s disease at diagnosis, in Armitage J, Diehl V, Flandrin G, et al (eds): Fifth International Symposium on Hodgkin's Lymphoma: Leukemia & Lymphoma, Koln, Germany, September 22-25, 2001, pp 15

23. Sureda A, Mataix R, Hernandez-Navarro F, 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 20:283-288, 1997

24. Moreau P, Fleury J, Brice P, 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 21:787-793, 1998

25. Nademanee A, Molina A, Fung H, 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 5:292-298, 1999

26. 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 86:1317-1318, 2001

27. Andre M, Henry-Amar M, Blaise D, et al: Treatment-related deaths and second cancer risk after autologous stem-cell transplantation for Hodgkin's disease. Blood 92:1933-1940, 1998