High-Dose Melphalan and Autologous Bone Marrow Transplantation as Consolidation in Previously Untreated Myeloma

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Purpose: **We report the results of intensive chemotherapy with high-dose melphalan (HDM) following conventional-dose cytoreductive chemotherapy in previously untreated patients with myeloma.**

Patients and Methods: **From 1986 to 1991, 53 previously untreated patients with myeloma received HDM 200 mg/m^2 plus methylprednisolone 1.5 g daily (MP) for 5 days with autologous bone marrow transplantation (ABMT) after cytoreductive chemotherapy.**

Results: **At the time of HDM administration, responses to induction therapy were complete remission (CR) in nine patients, partial remission (PR) in 38, and no response (NR) in six. Following HDM, all but one patient responded, with 40 patients achieving a CR (75%). There was one treatment-related death following HDM. The median time to reach a WBC count more than 1,000/μL and platelet count more than 25,000/μL was 19 days (range, 13 to 30) and 24 days (range, 15 to 55), respectively. The median duration of response has not been reached at 20 months, and it is significantly longer for patients in CR than for those in PR ($P < .025$). Currently, with a median follow-up duration of 31 months (range, 6 to 58), 12 patients are dead and 40 are alive, and the estimated probability of survival at 54 months is 63%. Multivariate analysis found hemoglobin (Hb) more than 10 g/dL ($P = .012$), and stage A disease ($P = .001$) at diagnosis to be favorable indicators for survival.**

Conclusion: **Myeloma patients who are able to receive HDM plus ABMT following conventional chemotherapy achieve a high proportion of CRs, which may be associated with prolonged survival.**

J Clin Oncol 12:759-763. © 1994 by American Society of Clinical Oncology.

MELPHALAN plus prednisolone (MP) remains the most widely used treatment for myeloma.[1] Combination chemotherapy regimens (alkylating agents with or without doxorubicin) have failed to increase consistently either the standard response rate of 50% to 60% or the median survival duration of 30 months that can be achieved with standard MP.[1,2]

In an attempt to improve these results, our strategy has been to escalate the dose of melphalan to take advantage of the steep dose-response curve for alkylating agents that has been demonstrated in vitro.[3] Early studies[4,5] with high-dose melphalan (HDM) 140 mg/m^2 without autologous bone marrow transplantation (ABMT) resulted in a response rate of 82%, including a 32% complete remission (CR) rate, and a recent update[6] of the original cohort has shown 35% of these patients to be alive at 9 years. A subsequent study[7] used vincristine, doxorubicin, and methylprednisolone (VAMP) as induction therapy to reduce tumor burden and the extent of marrow infiltration before the administration of HDM (140 to 200 mg/m^2). The overall response rate was 74%, with a 50% CR rate. When autologous bone marrow rescue was possible, the period of bone marrow suppression was reduced, despite the higher dose of melphalan (200 mg/m^2).

Other groups have used the same approach, and worldwide more than 400 myeloma patients[8] have received intensive treatment (alkylating agent with or without total-body irradiation [TBI]) with hemopoietic stem-cell support. The heterogeneity in patient selection and regimen used, and the low number of previously untreated patients, make it difficult to draw firm conclusions about the usefulness of intensive treatment as front-line therapy.

The objective of the present report is to describe the outcome of previously untreated patients who have received HDM with ABMT after induction therapy. Analysis of prognostic factors in relation to response, duration of remission, and survival are also performed for this highly selected group of patients.

PATIENTS AND METHODS

Between September 1986 and May 1991, 53 patients with multiple myeloma were considered eligible for treatment with HDM with ABMT after induction chemotherapy. These 53 patients were derived from a previously untreated group of 105 patients with myeloma who entered one of our high-dose programs and whose inclusion criteria were as follows: (1) age less than 65 years; (2) no prior chemotherapy; (3) no previous ischemic heart disease or chronic bronchitis; (4) glomerular filtration rate (GFR) more than 30 mL/min; (5) less than 30% bone marrow infiltration to maximum response to induction therapy; and (6) informed, signed consent. Thirty-two of 126 patients did not proceed to HDM due to progression or early death, and 20 received HDM without a graft because

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Submitted November 23, 1992; accepted December 3, 1993.

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0732-183X/94/1204-0017$3.00/0

of failure to clear the myeloma infiltration of the marrow down to 30% or less. A further 21 patients were excluded from this analysis as they received post-HDM maintenance interferon as part of a prospective randomized study.

Patients

Patient characteristics are listed in Table 1. The median age was 52 years (range, 30 to 69), with 34 men and 19 women. Performance status (PS) at diagnosis was less than 2 in 38 cases and ≥ 2 in 15. Patients were classified according to their myeloma-protein (immunoglobulin G [IgG]κ, 21; IgGλ, 12; IgAλ, four; Bence-Jones [BJ]κ, four; BJλ, five; nonsecretors, four) and to Durie-Salmon[9] staging system (IA, 10; IIA, two; IIIA, 34; IIIB, seven). The median value of serum β_2-microglobulin was 3.1 mg/L (range, 1.2 to 17).

Treatment

Thirty-two patients received VAMP as the induction regimen (vincristine 0.4 mg intravenously [IV] by continuous infusion [CI] every 24 hours for 4 days; doxorubicin 9 mg/m^2 IV every 24 hours for 4 days by CI; methylprednisolone 1.5 g IV or orally daily for 5 days). Weekly cyclophosphamide[10] (500 mg IV bolus on days 1, 8, and 15) was added to VAMP in 11 patients (C-VAMP), and 10 patients received cyclophosphamide and verapamil[11] (10 mg IV) every 24 hours by CI for 4 days (VC-VAMP). These regimens were administered every 3 weeks until CR was attained or until the paraprotein level had plateaued over two successive courses. The median number of cycles was five (range, two to 11).

Table 1. Patient Characteristics

No. of patients	53
Age (years)	
Median	52
Range	30-69
Sex	
Female	19
Male	34
PS	
0-1	38
2-4	15
Stage	
IA	10
IIA	2
IIIA	34
IIIB	7
Myeloma protein	
IgG	33
IgA	7
BJ	9
Nonsecretor	4
κ	28
λ	21
β_2-microglobulin	
Median	3.1
Range	1.2-17
Induction treatment	
VAMP	32
C-VAMP	11
VC-VAMP	10
Follow-up (months)	
Median	31+
Range	(6+-58+)

Six to 10 weeks after the last course of cytoreductive therapy, HDM (200 mg/m^2) was administered to patients who had received a priming dose[12] of cyclophosphamide (400 mg/m^2) 7 days previously. The bone marrow was harvested just before HDM and stored at 4°C. At that time, the percentage of marrow infiltration by plasma cells was 0% in 22 patients, 1% to 5% in 18 patients, and 6% to 30% in 13 patients. The median number of nucleated cells reinfused after HDM was 2×10^8/kg (range, 1 to 4.1×10^8). One patient received a reduced dose of melphalan (100 mg/m^2) because of a GFR of 35 mL/min. All patients received high-dose methylprednisolone 1.5 g IV or orally on days 1 to 5 for 5 days after marrow rescue.

A 7-day course of allopurinol was started on admission. Cimetidine and prophylactic amphotericin lozenges and nystatin were administered throughout the hospital course. A combination of gentamicin, piperacillin, and flucloxacillin was commenced on day 5 and changed when clinically indicated. Platelet support was administered while the count was less than 20×10^9/L or greater than this if there was evidence of bleeding.

Assessment

Our current response definitions were applied.[7] CR was defined as no measurable serum or urine paraprotein as measured by scanning densitometry of protein separated by electrophoresis and stained by Ponceau S, and 5% or fewer plasma cells of normal morphology in bone marrow aspirate for at least 3 months. Partial remission (PR) was defined as a more than 50% decrease in measurable paraprotein (IgG or IgA myeloma) or bone marrow infiltration (BJ or nonsecretory myeloma) sustained for ≥ 1 month. Relapse was defined as reappearance of myeloma protein or bone marrow infiltration more than 5% for patients in CR and a 25% increase in measurable paraprotein on two samples 1 month apart for patients in PR. No response (NR) was considered if the patient failed to achieve a CR or PR. Toxicity was specifically recorded by a trained observer in accordance with World Health Organization criteria.

Statistical Analysis

The duration of response was measured from the date of HDM. Survival was measured from the first cycle of induction therapy. Prognostic factors for response were analyzed by χ^2 tests.[13] The durations of actuarial response and survival were plotted using the Kaplan-Meier[14] method. Differences between the curves were analyzed using the log-rank test.[15] Multivariate analysis of survival was performed using a stepwise selection procedure and a proportional hazards regression model.[16]

RESULTS

Response and Duration of Remission

Fifty-two of 53 patients had a response to HDM (98%). Forty patients (75%) achieved a CR, including 27 of 38 patients who had a PR after induction chemotherapy and four of six who showed NR (Table 2). The median time to reach the best response after HDM was 99 days (range, 16 to 580). This analysis excluded patients who had already reached CR before receiving HDM. PS and pain

Table 2. Response to Induction Therapy and HDM Plus ABMT

Response	No. of Patients: Response to Induction	No. of Patients: Response Post-HDM
CR	9	40
PR	38	11
NR	6	1
Treatment-related death	—	1

grade returned to 0 in all but three patients and were abnormal (range, 1 to 4) in 43 patients before treatment. After HDM, the maximum grade was only 1. Forty-five patients had evidence of humoral immunosuppression before treatment, and 34 (75%) had complete normalization of their immunoglobulin levels. At the time of evaluation, 24 patients had relapsed and 28 remained in remission. The estimated median duration of response is 23 months, with 30% of patients free from progression at 36 months.

The following patient characteristics were examined in a multivariate analysis to assess their significance as prognostic factors for duration of remission: age (< 50 years *v* > 50 years), sex, PS (0 to 1 *v* 2 to 4), β_2-microglobulin (≤ 4 mg/L *v* > 4 mg/L) stage (A *v* B and I/II *v* III), myeloma paraprotein (IgG *v* no IgG), hemoglobin (Hb) (< 10 g/dL *v* ≥ 10 g/dL), creatinine level (normal *v* elevated), bone lesions (< three lesions *v* ≥ three lesions), percent plasma cell in bone marrow (< 30% *v* ≥ 30%), and response to induction treatment and to HDM (CR *v* PR *v* NR). None of these significantly affected the duration of remission, except CR following HDM (Fig 1), which was associated with a longer progression-free interval ($P < .025$).

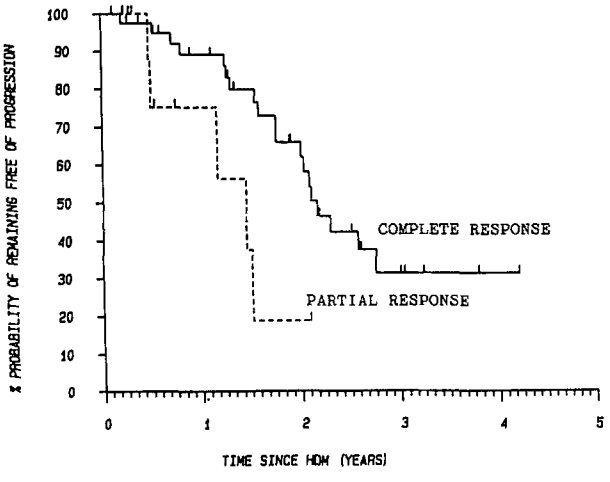

Fig 1. Progression-free survival curves, comparing patients in CR *v* PR. Difference is significant ($\chi^2 = 5.3$, $df = 1$, $P < .025$).

Survival

The median follow-up in this study was 31 months (range, 6 to 58) from the first cycle of induction therapy. The minimum follow-up time from HDM was 43 days. Twelve patients have died, the causes of death being as follows: early toxic death after HDM (one case), progressive disease (five cases), bone marrow failure after high-dose busulfan for relapsed disease with or without infection (five cases), and second malignancy (one case). The median survival duration has not yet been reached, but 63% of patients are expected to be alive at 54 months (Fig 2).

When multivariate analysis of the same factors that were analyzed for response were analyzed for survival those that showed favorable prognostic significance were Hb more than 10 g/dL ($P = .012$) and stage A disease ($P = .001$).

Follow-Up

Second malignancies were documented in two patients who were in continuous CR. One patient developed myelodysplastic changes in his marrow and, eventually, acute myeloid leukaemia (AML) 18 months following HDM. Another patient presented with a substernal plasmacytoma in 1983 and received local radiation. In June 1987, her disease progressed to multiple myeloma and she was entered onto our protocol after further radiotherapy to a new left supraclavicular fossae plasmacytoma. Finally, in 1991, she presented with a new mass in the left supraclavicular area, which, after biopsy, was classified as undifferentiated lymphoma and responded poorly to chemotherapy.

Toxicity

The WBC count remained less than 1×10^9/L for 7 to 22 days (median, 12) after bone marrow infusion. The

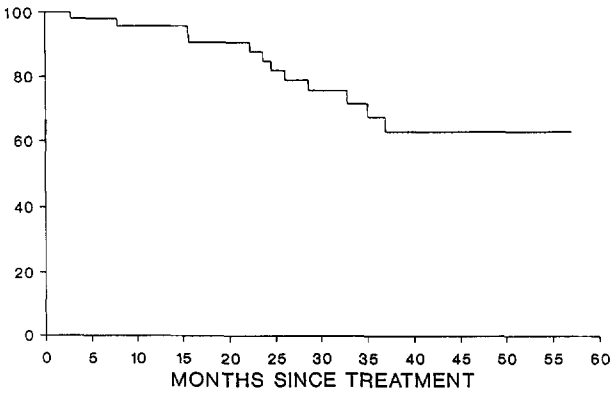

Fig 2. Actuarial survival of the whole group (N = 53).

median time to development of grade IV leukopenia was 7 days (range, 5 to 9) with recovery at 19 days (range, 13 to 30). The median period of platelet count less than 25×10^9/L was 13 days (range, 5 to 44), starting on day 10 (range, 7 to 14) and finishing on day 24 (range, 15 to 55) after ABMT.

All patients developed fever during the course of treatment, and infection was clinically evident in 16 cases, including four septicemia (*Streptococcus faecium, Pseudomonae aeuragiosa, Escherichia coli,* and organism unidentified), six central-line infections (*Staphylococcus epidermis* isolated in three cases), and six chest infections (one *Streptococcus,* one *Aspergillus,* two suspected fungus infections, two unknown). Only one early death was recorded at day 82, due to septicemia with concomitant renal and marrow failure.

Extramedullary toxicity (Table 3) was mainly gastrointestinal (nausea, vomiting, and diarrhea), anorexia, and stomatitis (grade II and III). All patients had universal alopecia (grade III) starting on day 13 (range, 10 to 17) post-ABMT.

DISCUSSION

This report represents the largest series of patients with myeloma treated with intensive chemotherapy with ABMT as consolidation after induction treatment. It includes 53 previously untreated patients who entered consecutive protocols of initial induction therapy (VAMP ± C ± V) followed by consolidation with HDM and ABMT. The purpose of this study was to examine outcome in this highly selected group of patients, who were able to receive intensive consolidation treatment after conventional-dose induction chemotherapy. The patients are a highly selected group in that they completed induction therapy and had a sufficiently low level of bone marrow infiltration to allow ABMT. However, 77% did have advanced stage disease (stage IIIA or IIIB) at presentation. A comparison of the induction therapies used will be the subject of a future analysis.

The impressive response rate (98%), with 75% CRs, confirms previous observations of the direct relation between dose-intensity of melphalan and number and degree of responses.[5,17] Five of six patients judged to have primary resistant disease to VAMP entered remission (four CRs, one PR), and 27 of 38 PRs converted to CRs after HDM. This concurs well with reported experiences of overcoming resistance to VAD or VAMP in relapsed patients using HDM with or without TBI (40% to 80% response rate).[18,19] In vitro observations suggest that the mechanism of resistance to melphalan[20] differs from that found in vinca alkaloids and anthracyclines.

Table 3. Extramedullary Toxicity

Toxicity	Grade				
	0	I	II	III	IV
Nausea and vomiting	7	15	11	18	2
Anorexia	1	1	15	33	3
Mucositis	2	6	17	27	1
Diarrhea	9	10	22	11	1
Alopecia	—	—	—	53	—

Immediate benefits achieved in responding patients were a normalization in PS and pain grade in all but three patients, and reversal of humoral immunosuppression in 75% of patients. Overall, the expected median duration of remission is 24 months, which is superior to that achieved with standard chemotherapy[1] or maintenance interferon-α (IFN-α).[21] This interval was longer for patients in CR than for those in PR (26 *v* 17 months), and no other factor appears to be of significance.

HDM (200 mg/m^2), when administered with ABMT, is associated with severe but reversible acute extramedullary toxicity (anorexia, alopecia, mucositis), but less hematologic depression compared with lower doses of melphalan (140 mg/m^2) without ABMT[5] or with TBI and marrow support.[19] Moreover, only one episode of toxic death was recorded in our group.

The association of higher CR rate,[19] reduced acute toxicity, and the possibility of a successful second course at relapse[18] prompt us to recommend HDM as the best choice in myeloma consolidation therapy.

We have not used in vitro purging methods because of the lack of proven efficacy, although they appear not to compromise the autograft.[22] The role of hematologic growth factors has yet to be defined in this setting, but granulocyte-macrophage colony-stimulating factor[23] seems to accelerate marrow recovery after melphalan 100 mg/m^2 without graft support. There are encouraging experiences[24] with peripheral stem-cell support after intensive therapy, and this may represent an alternative rescue when ABMT is not feasible, eg, if there has been prior pelvic radiotherapy or extensive bone disease.

Two cases of second tumor have been observed. The first patient developed AML 18 months after HDM, and the other an undifferentiated lymphoma in the bed of prior radiotherapy 4 years after the ABMT. Although long-term follow-up data[6] from our first series of 63 patients suggest a decreased risk of AML in 4-year survivors as compared with those who have had continuous administration of melphalan,[25] the number of second malignancies in myeloma patients will be monitored as more effective therapeutic approaches are used.

To date, with a median follow-up duration of 31

months, the median survival duration has not been reached, and the estimated 63% survival rate at 54 months is unprecedented. Known prognostic factors,[26] such as stage and hemoglobin level at diagnosis, significantly influenced the outcome of the whole group. Interestingly, the outcome of patients with primary resistant disease was the same as that of those who responded to induction chemotherapy, provided that CR was achieved with HDM and ABMT.

As previously stated, IFN-α[21] administration maintains remission and increases survival in patients who respond to conventional therapy. To ascertain whether primary intensive and maintenance treatment have an additive effect, our group is currently conducting a randomized trial with IFN-α administered after recovery from HDM. Using the same approach, Attal et al[27] have reported a considerable increase in the projected disease-free survival rate (85% at 2 years), especially when CR was achieved. This was a nonrandomized study, wherein 20 patients received IFN-α after HDM plus TBI supported by ABMT.

In conclusion, HDM and ABMT after induction therapy produces response in practically all patients; CR is achieved in greater than 75% of patients, and toxicity is both predictable and manageable. A considerable increase in duration of remission and survival is found, with the effect being most marked in those patients who reach CR.

ACKNOWLEDGMENT

We acknowledge Professor T.J. McElwain, who pioneered these studies with HDM at the Royal Marsden Hospital and who died on November 26, 1990.

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