High-Risk Multiple Myeloma Treated With High-Dose Melphalan

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Purpose: This study was undertaken to evaluate the efficacy and toxicity of high-dose melphalan (HDM) 140 mg/m² in poor-risk multiple myeloma (MM).

Patients and Methods: Thirteen patients were previously untreated, and 13 had been pretreated with vincristine, Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH), and dexamethasone (VAD) for refractory or relapsed MM.

Results: All 11 fully assessed, untreated patients responded, and six achieved a complete response. Remissions were of excellent quality, but response duration—a median of 16 months—was short. This was probably due to the high incidence of unfavorable prognostic signs, like a high beta$_2$-microglobulin (B2M) and/or a high plasma cell labeling index (LI). None of the nine pretreated patients with a measurable M component had more than 50% reduction of M component after HDM, indicating that intensive treatment has no effect on a residual tumor population. The relapse-free period after HDM in this group of patients (median, 9 months) was not better than in a historical control group of patients treated with VAD alone. The major complications due to the prolonged myelosuppression were severe infections. After primary HDM, median time to recovery to greater than 0.5×10^9 granulocytes was 30 days; in previously treated patients, the recovery period was even longer. There were three toxic deaths. Fulminant relapses with features of J-chain disease were frequently observed, indicating a dedifferentiated tumor, probably induced or selected by the HDM.

Conclusions: HDM is an effective treatment resulting in good remissions for untreated MM. However, other therapy strategies should be explored first, focusing on the reduction of toxicity and prolongation of the relapse-free period, before HDM can be recommended as first-line treatment for the younger MM patient.

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THE PROGNOSIS FOR patients with multiple myeloma (MM) has hardly improved since the introduction of alkylating agents almost 30 years ago. Various treatment combinations with melphalan, prednisone, or cyclophosphamide, and one or more additional agents including anthracyclines have been used. However, median survival of patients with MM is still about 30 to 36 months after diagnosis.[1,2] When unfavorable prognostic signs are present, such as a high beta$_2$-microglobulin (B2M) or a high plasma-cell growth fraction, survival is reduced to between 8 and 18 months.[3-5] The prognosis for patients who are primarily resistant or who have become refractory to first-line treatment is even worse.[6] Although the vincristine, Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH), and dexamethasone (VAD) regimen produces responses in about 60% of these patients, response duration is short; most patients relapse within 1 year.[7,8]

Two promising approaches have been introduced recently: the use of high-dose melphalan (HDM) and the introduction of several biologic response modifiers, of which interferon is the most well known.[9,10] We report our experience with HDM 140 mg/m² in a group of treated and pretreated high-risk MM patients.

PATIENTS AND METHODS

From February 1985 until January 1990, previously untreated patients with multiple myeloma under age 65 years and with a high tumor mass (stage III according to the staging system reported by Durie and Salmon[11]) and patients under age 65 years with a response to second-line therapy that consisted of VAD were entered onto a study with intravenous HDM 140 mg/m². All patients had a creatinine clearance greater than 40 mL/min. No patient was excluded because of renal insufficiency in this period.

All patients had routine evaluations before treatment, including physical examination, skeletal x-ray, bone marrow aspirate, bone marrow biopsy, and myeloma protein, serum B2M, lactate dehydrogenase (LDH), and albumin measurements. For immunofluorescence staining of the plasma cells, mononuclear cells were separated from the bone marrow on Ficoll-hypaque. Slides were prepared with a cytocentrifuge. After fixation of the cells, they were stained with purified fluorescein isothiocynate (FITC) or tetramethylrhodamine isothyocyanate (TRITC)-conjugated H chain antibodies (α, γ, μ) and with L chain conjugates (κ, λ). The plasma-cell labeling index (LI) was performed with bromodeoxyuridine (BRDU) in a double fluorescence technique.[12]

As shown in Table 1, 26 patients, median age 55 years, were treated. Most untreated patients had one or more unfavorable prognostic signs, eg, high B2M or a high LI. In eight patients B2M was more than 6 mg/L; in four patients, the LI was more than 3%. Serum albumin under 30 g/L was not present in any of the patients; the LDH level was over 500 U/L in only one patient. A complete response (CR) after VAD and HDM was determined as complete

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Table 1. Characteristics of Patients With MM Treated With HDM

	Previously Untreated (n = 13)	Previously Treated (n = 13)*
Median age, years (range)	58 (44-65)	53 (32-60)
Sex (male/female)	5/8	7/6
Immunoglobulin G	10	7
Immunoglobulin A	2	2
Immunoglobulin D	0	1
BJP	1	3
Stage IIIA	13	
B2M > 6 mg/L	8	
LI > 3%	4	
B2M and LI > 3	2	
LDH > 500 U/L	1	
Albumin < 30 g/L	0	
Performance status (ECOG)		
0	0	3
1	4	8
2	5	2
3	4	0
4	0	0

Abbreviation: BJP, Bence Jones proteinuria.

*Four patients were refractory to melphalan and prednisone; five relapsed during and four relapsed after melphalan and prednisone. Three patients had a CR, seven a PR, and three a minor response after VAD. Median number of VAD courses was five (range, 3 to 11 courses) and median time of follow-up before HDM was 20 months (range, 9 to 31 months).

disappearance of myeloma proteins, as determined by immunofixation of serum and/or concentrated (10 ×) urine, and normalization of the bone marrow, including less than 5% plasma cells in a representative bone marrow biopsy and less than 5% plasma cells in a normocellular bone marrow aspirate. The plasma cells should be polyclonal after immunofluorescent staining. A partial response (PR) was identified as a more than 50% reduction of myeloma proteins and a minor response, between 25% and 50% reduction of M component.

Response and survival curves after HDM were calculated using the method of Kaplan and Meier.[13] Performance status was determined according to the criteria of the Eastern Cooperative Oncology Group (ECOG)[14]: 0, normal; 1, ambulant with symptoms; 2, bedrest less than 50% of the day; 3, bedrest greater than 50% of the day; 4, bedrest all day.

Patients were treated in a single room. A central indwelling catheter was used for intravenous (IV) infusions and blood sampling. Melphalan 140 mg/m^2 was given as a slow bolus injection with a forced saline diuresis. Diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg, and metoclopramide 1 mg/kg IV were administered 1 hour before and 6 hours after HDM, providing effective antiemesis. Selective decontamination of the alimentary tract was started the week before HDM and consisted of oral ciprofloxacin 500 mg twice daily and amphotericin B suspensions and tablets. In addition, amphotericin B was given IV every other day at a dose of 0.4 mg/kg body weight prophylactically when the neutrophil count was below 0.5 × 10^9/L. Final evaluation was dated June 1, 1991.

RESULTS

Primary HDM

All 11 assessable patients showed a response; six had a CR, five patients entered a PR. Two patients died during the aplastic period after HDM: one patient on day 28 due to interstitial pneumonia (no specific cause was found in broncheolar alveolar lavage and postmortem examination), and the other patient on day 21 due to overwhelming septicemia caused by enterococci. Postmortem examination showed severe mucositis of the entire digestive tract. All other patients showed a remarkable improvement in their performance status and in other parameters such as pain grade and anemia. Normalization of hemoglobin occurred in all seven patients with anemia. Only three patients complained of residual minor nonspecific pain, and none of these patients required specific analgesia. Most patients were able to perform their normal daily activities. In three patients minor radiographic bone healing was observed, and in nine patients complete recovery of polyclonal humoral immunoglobulins occurred. The results of primary treatment with HDM are listed in Table 2.

Eight patients have relapsed: all five patients with a PR and three of the six patients with a CR. In three patients extramedullary relapse preceded bone marrow relapse. Median follow-up is 27 months (range, 17 to 41+ months). Median response duration is 16 months (Fig 1). One patient died after 29 months due to fulminant disease. Median survival has not been reached yet (Fig 2). None of the relapsed patients was given a second dose of induction with HDM.

Consolidation HDM

Thirteen patients received HDM after a response to VAD chemotherapy. None of nine patients with a still-present M component after VAD had more than a 50% reduction in the M component. In seven patients the M component was lower after treatment (median, 28%; range, 8% to 44%), and in two patients the M component remained unchanged. One patient died suddenly, within 1 month after HDM, due to pulmonary hemorrhage. Postmortem examination showed a rupture of the pulmonary artery due to invasive aspergillosis. Eleven of the remaining 12 patients have relapsed after HDM, including the three patients in CR after VAD with no measurable M component and immunomorphologically normal bone marrow. These three relapsed at 4, 4, and 30 months, respectively. In three patients extramedullary relapses preceded a fulminant bone marrow relapse. Median time to relapse was 9

Table 2. HDM in Previously Untreated MM: Clinical Outcome

Patient No.	B2M > 6 mg/L	LI > 3%	Response	Response (months)	Survival (months)	Performance Before HDM	Status After HDM	Bone Healing	Recovery (humoral Ig)
1	–	–	CR	28	41+	2	0	+	+
2	–	+	PR	17	34+	2	0	–	–
3	–	–	CR	31+	31+	2	0	–	+
4	+	–	CR	30+	30+	2	0	+	+
5	+	–	CR	17	29	3	1	–	+
6	+	–	PR	12	27+	1	0	–	–
7	+	–	CR	24+	24+	3	0	–	+
8	+	–	PR	9	23+	3	1	–	–
9	–	–	CR	16	21+	2	0	+	+
10	+	+	PR	12	18+	3	1	–	–
11	–	+	PR	5	17+	1	1	–	–
12	+	+	ED	NA	0	2	NA	NA	NA
13	+	–	ED	NA	0	3	NA	NA	NA

Abbreviations: ED, early death; NA, nonassessable.

months (Fig 1); median survival was 26 months (range, 11 to 60+ months; Fig 2).

Bone healing and/or restoration of humoral immune deficiency was not observed in this group of pretreated patients. The results of HDM consolidation treatment are shown in Table 3.

Toxicity of HDM

Most patients experienced nausea and vomiting (World Health Organization [WHO] grade 2) during the first days after HDM, but good control of these complications was achieved with conventional antiemetics. Diarrhea (WHO grade 2) lasting for a few days and mucositis (WHO grade 2 to 3) lasting for 1 or 2 weeks started approximately 1 week after treatment. In one patient, mucositis grade 4 was observed. Complete but reversible alopecia occurred in all patients (Table 4). The major toxicity-related problem after HDM was prolonged myelosuppression. In previously untreated patients, median time to recovery to greater than 0.5×10^9 granulocytes per liter was 30 days (range, 27 to 35 days) and to greater than 30×10^9 platelets per liter, 31 days (range, 25 to 35 days). In previously treated patients, bone marrow recovery was even slower: median time to recovery to greater than 0.5×10^9 granulocytes per liter was 36 days (range, 31 to 55 days), and to greater than 30×10^9 platelets per liter, 40 days (range, 31 to 70 days).

As a result of the prolonged myelosuppression, complicating infections such as pneumonia (seven patients) and bacteremias (18 patients) were experienced. Most bacterial infections were due to gram-positive organisms (16; one fatal), of which about 50% were central line-related. In the first eight patients, five required treatment with IV amphotericin B because of suspected systemic fungal infection. Therefore, we modified our standard antiinfection prophylaxis, adding IV amphoter-

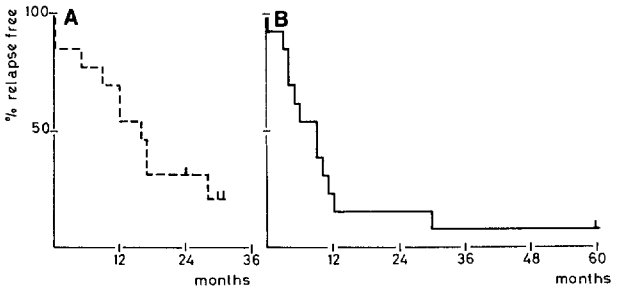

Fig 1. (A) Patients treated with primary HDM; probability of remaining in remission for patients in CR or PR. (B) Patients treated with consolidation HDM after a response to VAD chemotherapy. Probability of remaining in PR or CR from the start of HDM treatment.

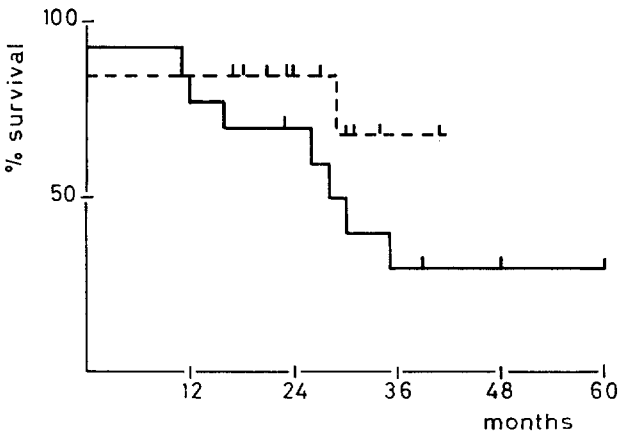

Fig 2. (---) Patients treated with primary HDM. Probability of survival from the start of treatment. (—) Patients treated with consolidation HDM after a response to VAD chemotherapy. Probability of survival from the start of HDM treatment.

Table 3. HDM in Previously Treated Patients: Clinical Outcome

Patient No.	Follow-Up Pre-HDM (months)*	Response to VAD	Relapse-Free Post-HDM (months)	Survival (months)	M Component (g/L)		% Decrease in M Component Post-HDM
					Pre-HDM	Post-HDM	
14	9	PR	60	60+	23	14	39
15	12	CR	30	48+	0	0	NA
16	16	MR	6	39+	33	25	24
17	24	PR	12	35	21	15	28
18	21	MR	3	30	14	8	43
19	31	MR	10	28	25	23	8
20	20	PR	11	26+	28	18	35
21	9	PR	9	23+	26	26	0
22	21	CR	4	16+	0	0	NA
23	12	CR	4	16	0	0	NA
24	24	PR	5	12	15	15	0
25	26	PR	9	11	20	16	20
26	48	PR	ED	0			NA

Abbreviation: MR, mixed response.

*Patients no. 14, 15, 21, and 22 were primary refractory to melphalan and prednisone. Patients no. 16, 17, 18, 19, and 23 relapsed during treatment. Patients no. 20, 24, 25, and 26 were on treatment when they relapsed.

icin B 0.4 mg/kg body weight during the granulocytopenic period. This was administered to all patients every other day. Thereafter, only one systemic fungal infection occurred in 18 patients. We observed three early deaths: one due to interstitial pneumonia, one due to severe mucositis with subsequent septicemia, and one due to invasive aspergillosis.

DISCUSSION

HDM is an effective therapy for previously untreated MM as far as response rate and improvement of performance are concerned: all 11 fully assessed patients in our study responded, with six achieving a CR. No failure was observed in this group. However, response duration was disappointing. In the study by McElwain and Powles,[9] response duration was about 18 months. Our group of patients was in a similar range, ie, 16 months. A high incidence of unfavorable signs may have influenced this outcome: most patients had a high B2M or a high LI, or both. Advantages of HDM in high-risk untreated MM are prolonged survival (median survival has not yet been reached in our group) and an improvement in the quality of life during the remission; all patients were able to perform normal activities again, and analgesics were not needed. Radiographic signs of bone healing were observed in a minority (three of 11), but reversal of humoral immunodeficiency occurred in most patients (nine of 11). A disadvantage of HDM is the considerable toxicity. There were three early deaths (11%): two of 13 patients treated with primary HDM and one of 13 patients treated with consolidation HDM. Major infective complications due to prolonged severe myelosuppression were experienced. The median time to recovery to greater than 0.5×10^9 granulocytes per liter was 30 days after primary HDM. In previously treated patients, the recovery period was even longer (36 days). This confirms reports by others[15,16] that HDM is difficult to manage, especially in pretreated patients.

Table 4. Toxicity of HDM (N = 26)

	WHO Grade			
	1	2	3	4
Nausea, vomiting	4	16	5	1
Diarrhea	14	10	1	1
Alopecia	0	0	0	26
Infections	0	9	15	2

HDM does not seem to have a major effect on a residual plasma-cell population after previous chemotherapy. In a recent study, only 50% of 34 VAD-responsive patients obtained significant cytoreduction after HDM plus total body irradiation (TBI) and autologous bone marrow transplantation (ABMT).[17] We also found no significant reduction in tumor load, as reflected by the M component, when HDM was given as consolidation treatment after VAD for refractory and relapsed myeloma. The relapse-free period (median, 11 months) in this group of patients was no better than in a control group of patients treated with VAD alone.[8]

A new phenomenon was fulminant relapse after HDM, observed in six patients. Six of the 17 relapses had transformed into so-called nonproducing myeloma with features of J chain disease.[18] These patients had very high tumor-growth fractions. In six patients extramedullary relapses (including skin, pancreas, and breast)

preceded bone marrow relapses. This indicates a dedifferentiated tumor, probably induced or selected by the HDM, with high resistance to chemotherapy.

Unfortunately, the remissions after HDM are short, and the development of new treatment strategies should be encouraged. It is debatable if the relapse-free period can be prolonged by the use of even higher doses of cytotoxic drugs, or the combination of HDM with TBI. In a 1989 study with 200 mg/m^2 melphalan and bone marrow rescue, more CRs were achieved (± 50%), but the relapse-free periods were not prolonged.[19] In a recent study by Jagannath et al,[17] 55 pretreated patients underwent ABMT after HDM or thiotepa with TBI, but the median relapse-free period was only 15 months. Patients with a high B2M level had a very short remission period.

As yet there is no effective treatment against the clonogenic myeloma cell. It appears to be unresponsive to allogeneic bone marrow transplantation[20] or to purging with monoclonal antibodies.[21] Plasma-cell purging may be also insufficient, as the myeloma stem cell is probably not a mature plasma cell but a preplasma cell[22] or an immature B cell.[23]

The bone marrow toxicity of HDM might be reduced by the combination of hematopoietic growth factors granulocyte (macrophage)—colony-stimulating factor (G[M]-CSF) and interleukin-3. This approach (HDM with GM-CSF) is under investigation in a randomized multicenter trial in Europe. Maintenance therapy with interferon alfa (as opposed to intensive follow-up treatment) after response to HDM may help to prolong remission time.

In conclusion, HDM is the most effective induction treatment available, even for unfavorable multiple myeloma. However, the toxicity is considerable, and remissions, though of excellent quality, are not sustained. It therefore remains questionable whether HDM should be recommended as first-line treatment for the younger MM patient. Based on our results, consolidation HDM could not be recommended.

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