

High-Dose Melphalan and Granulocyte-Macrophage Colony-Stimulating Factor for Refractory Multiple Myeloma

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High-dose melphalan has induced remissions in about 40% of patients with refractory myeloma, but the mortality has been high, at about 20%, due to complications of prolonged granulocytopenia. In an attempt to stimulate earlier granulocyte recovery, recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) was administered subcutaneously to 23 patients with refractory myeloma who had been treated with melphalan at a high dose of 100 mg/m². Thirty-nine percent of patients achieved marked tumor cytorreduction by at least 75%. 2 died within 2 months from infectious complications during severe neutropenia; and median durations of relapse-free and overall survival were 7 and 10+ months, respectively. The nine patients presenting with both advanced age over 50 years and a long history of prior therapy of over 1 year required significantly longer median times of 31 days for granulocytes and of 63 days for platelets to reach safe levels of at least 500/ μ L and 50,000/ μ L, respectively, than the 14 remaining patients who had none or only one of

these adverse features (21 and 26 days, respectively). In a historic control of 43 patients treated previously with high-dose melphalan but without GM-CSF, hematologic recovery to the aforementioned levels of granulocytes and platelets proceeded over almost 5 weeks, regardless of age and prior treatment exposure. Thus GM-CSF seems to hasten marrow recovery, especially in patients with adequate normal marrow stem-cell reserve as defined by younger age or less prior therapy. While not shortening the duration of neutropenia, GM-CSF dose increments (from 0.25 to 0.5 to 0.75 mg/m²) increased the incidence of severe toxicity from 0% to almost 40%, especially among older patients. These results support the usefulness of low-dose GM-CSF (0.25 mg/m²) in stimulating marrow recovery in selected patients with adequate marrow reserve treated with high-dose melphalan for refractory multiple myeloma.

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MELPHALAN AND prednisone in standard doses have been the mainstay of therapy for multiple myeloma for over 20 years, inducing remissions in about one half of patients and providing a median survival of about 3 years.¹ When resistance to melphalan-prednisone develops, a regimen combining continuous infusions of vincristine and adriamycin with high doses of dexamethasone (VAD) reestablished disease control in approximately 40% of patients.² In case of additional resistance to VAD, high-dose melphalan (HDM) was effective in about 40% of patients, but prolonged marrow-aplasia led to fatal infections in about 20%.³ To induce earlier granulocyte recovery after HDM, a clinical trial was designed to evaluate the role of granulocyte-macrophage colony-stimulating factor (GM-CSF), a recombinant hematopoietin with major proliferative and differentiating effects on granulocytic and monocytic lineages.^{4,5} In comparison with a group of 43 patients who had previously received HDM alone, added GM-CSF hastened hematologic recovery, especially of granulocytes but primarily in younger patients with limited prior drug exposure.

MATERIALS AND METHODS

Twenty-three patients with refractory myeloma were enrolled in a trial to examine whether daily subcutaneous administration of GM-CSF would speed up hematologic recovery after intravenous (IV) HDM at a dose of 100 mg/m². Eligibility criteria included good performance (Zubrod score less than 3) and no major renal function impairment (creatinine less than 3 mg%), which had been established as favorable features for survival in a previous trial of 43 patients receiving HDM without GM-CSF.³

Tables 1 and 2 summarize the characteristics of patients treated with HDM with GM-CSF. Approximately one half was older than 50 years, had extensive marrow plasmacytosis greater than 30%, and had been treated for over 1 year. The median number of prior treatment regimens was two; about 80% were refractory to alkylating agents and to VAD; three had even received high-dose therapy requiring autologous hematopoietic stem cell support (marrow, one patient; blood stem cells, two patients). Radiotherapy to marrow-

containing bones such as spine and pelvis had been given to almost 40%. Myeloma staging (serum beta-2-microglobulin, B2M)⁶ and assessment of disease aggressiveness (serum lactic dehydrogenase, LDH)⁷ indicated unfavorable features for survival in no more than one quarter of patients.³ Adverse features for responsiveness to therapy (low DNA and RNA content) were present in 30%.⁸

After a written informed consent was obtained in accordance with institutional policy, a single IV infusion of HDM (100 mg/m²) was given in 100 mL of dextrose and water over 30 minutes, after premedication with 100 mg of dexamethasone as well as metoclopramide (40 mg) and diphenhydramine hydrochloride (25 mg). Melphalan was provided by Burroughs-Wellcome (Research Triangle Park, NC). GM-CSF, provided by Schering-Plough (Kenilworth, NJ), was given subcutaneously starting 3 days after melphalan at an initial dose of 0.25 mg/m², with weekly escalation by 0.25 mg/m² to a maximum of 0.75 mg/m² if neutropenia less than 500/ μ L persisted. Eleven patients were started at the lowest dose level of 0.25 mg/m², and 12 received 0.5 mg/m² as their initial dose. GM-CSF was discontinued whenever granulocyte counts exceeded 2,000/ μ L.

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Submitted December 11, 1989; accepted April 25, 1990.

Supported in part by Grants No. CA 37161 and CA 16672 from the National Cancer Institute, Bethesda, MD.

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0006-4971/90/7604-0021\$3.00/0

Table 1. Patient and Disease Characteristics

Parameter	N
Total	23
Male	19
Age >50 years	11
Zubrod performance > 1	3
Serum creatinine > 1.4 mg%	4
Serum beta-2-microglobulin > 6 mg/L	6
Serum lactic dehydrogenase > 300 U/L	4
Marrow plasma cells > 30%	12
Plasma cells hypodiploid or with low RNA index ≤ 4	7

on 3 successive days. Antibiotic prophylaxis consisted of trimethoprim-sulfamethoxazole (160 mg/800 mg; given twice a day, every other day) or, in case of drug allergy, of ciprofloxacin (750 mg given twice a day, every other day). When overt infection developed, IV broad-spectrum antibiotics were instituted.

Serial assessments of myeloma protein and bone marrow plasmacytosis were conducted to define remission. Clinical response was defined by 75% or greater reduction of myeloma protein synthesis⁹; complete remission required the disappearance of myeloma protein on immunofixation studies. Responding patients were followed on no treatment until relapse. Relapse-free survival and overall survival times were calculated by life-table analysis from the onset of treatment.

Statistical methods included χ^2 tests for comparison of rates¹⁰; Kaplan-Meier estimates¹¹ of relapse-free survival and survival curves; and generalized Wilcoxon tests¹² for comparison of curves.

To relate the results of GM-CSF-supported HDM to those observed in 43 previous patients with advanced and refractory myeloma receiving HDM without GM-CSF,³ their hematologic recovery patterns were examined in relationship to age and duration of prior therapy, the two features noted to affect the durations of granulocytopenia and thrombocytopenia after HDM with added GM-CSF.

RESULTS

Nine of 23 patients (39%) treated with HDM and GM-CSF achieved a calculated tumor regression of at least 75%, two of whom have relapsed 3 and 4 months after HDM; and six patients have died (Table 3). The median durations of relapse-free and overall survival were 7 and 10+ months, respectively. Two patients died on days 18 and 24 after

Table 2. Prior Treatment History

Parameter	N
Total	23
≥2 prior regimens	15
MP or VMCP-VBAP	18
VAD	19
High-dose therapy with autologous stem-cell support	3
Radiotherapy to spine or pelvis	9
> 12 months from first treatment	12
Never responded	6

Abbreviations: MP, melphalan, prednisone; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; VBAP, vincristine, BCNU, Adriamycin, prednisone.

Table 3. Clinical Outcome

Parameter	N
Early death within 2 months	2
Responding	9
Surviving	17
Median months relapse free	7
Median months surviving	10+

HDM from systemic aspergillosis when granulocyte levels were still under 100/ μ L; both patients had serum creatinine elevations above 2.5 mg% before HDM, and one was 78-years-old. The four remaining deaths occurred between 3 and 6 months after HDM and were due to disease progression.

Granulocytes recovered to greater than 500/ μ L after a median of 25 days, and the median time to a platelet count exceeding 50,000/ μ L was 32 days (Fig 1). One third of patients had a total white blood cell (WBC) count of less than 200/ μ L for more than 5 days. Pneumonia and/or sepsis were documented in 15 of 23 patients. The median duration of hospitalization was 4 weeks. Of six patients receiving HDM in the outpatient clinic, only one required hospital admission upon onset of neutropenic fever for intravenous (IV) antibiotics.

Multiple pretreatment variables that might affect the speed of hematologic recovery were examined. Recovery of platelets (greater than 50,000/ μ L) and, less markedly, of granulocytes (greater than 500/ μ L) proceeded faster in patients ≤50 years and in those treated within 12 months of their primary therapy (Table 4). Similarly, milder degree of anemia (hemoglobin greater than 10 g%) was associated with significantly earlier platelet recovery within 3 weeks as opposed to over 8 weeks in the more severely anemic patients. None of the other pretreatment variables, including those associated with tumor mass, extent of marrow plasmacytosis, type and number of prior treatment regimens, and renal function were associated with the duration of cytopenia after HDM; similarly, the GM-CSF starting dose did not influence the speed of hematologic recovery.

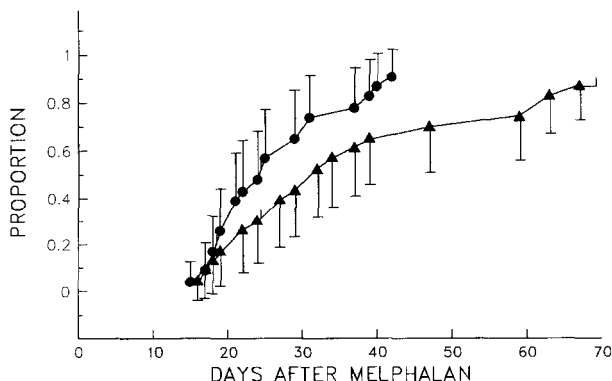


Fig 1. Median days with 95% confidence intervals to granulocyte levels greater than 500/ μ L (●) and to platelets greater than 50,000/ μ L (▲) after administration of melphalan 100 mg/ m^2 with GM-CSF for refractory myeloma (n = 23).

Table 4. Hematologic Recovery After High-Dose Melphalan + GM-CSF

Parameter	N	Median Days to			
		Granulocytes >500/ μ L	P	Platelets >50,000/ μ L	P
Age (yrs)					
≤50	12	21	.07	25	.02
>50	11	29		47	
Months from 1st Treatment					
≤12	10	21	.01	22	.0001
>12	13	31		59	
Hemoglobin (g%)					
≤10	13	29	.2	59	.0004
>10	10	21		23	
Age >50 and >12 mos from first treatment	9	31	.03	63	.009
Other	14	21		26	

Among the 23 patients receiving HDM with GM-CSF, the concurrence of advanced age (greater than 50 years) and extensive prior therapy (greater than 1 year) identified a poor risk group of nine patients in whom granulocyte and platelet recoveries were markedly delayed compared with those lacking both adverse features (Table 4 and Fig 2). The median times to granulocyte counts exceeding 500/ μ L and to platelet counts exceeding 50,000/ μ L among 43 patients treated previously without GM-CSF were 35 and 32 days, respectively, independent of age and duration of prior treat-

ment exposure. Among comparable patients up to age 50 years and/or with prior therapy not exceeding 12 months (applying to 24 of the previous trial without GM-CSF and to 14 of the current trial), GM-CSF shortened median granulocyte recovery from 35 to 21 days ($P = .0001$) and platelet recovery from 31 to 26 days ($P = .2$).

HDM produced mild nausea and only occasional vomiting when antiemetic prophylaxis was given. Toxicity attributed to GM-CSF included rash (three patients), diarrhea (eight patients), nausea and vomiting (eight patients), bone pain (five patients), temperature elevation to $\geq 39.5^{\circ}\text{C}$ (10 patients), and capillary leak syndrome with pericardial effusion (one patient, 78-years-old, with serum creatinine greater than 2.5 mg% and death from pulmonary aspergillosis on day 18). The incidence of toxicity was dose related, so that none of the 11 patients receiving the lowest dose of 0.25 mg/ m^2 had grade 3 or 4 extramedullary toxicity, compared with 18% of those receiving 0.5 mg/ m^2 and 38% of those receiving 0.75 mg/ m^2 ($P = .01$). Thus GM-CSF dose reduction or interruption was required in 4 of 22 patients who received 0.5 mg/ m^2 and in 9 of 18 patients who received 0.75 mg/ m^2 ($P = .07$). Except for those treated at the lowest dose of 0.25 mg/ m^2 , more patients over age 50 years experienced grade 3 and 4 GM-CSF-related toxicity (64%) than younger patients (25%, $P = .1$).

DISCUSSION

IV-administered HDM is emerging as a useful therapy for both refractory and newly diagnosed myeloma.^{3,13} The present study was designed to assess the role of GM-CSF in patients who are most likely to benefit from HDM (ie, those with good performance and relatively normal renal function); such patients had a median survival of about 1 year in the earlier trial of 43 not receiving GM-CSF.³ About 40% of patients in the current study have responded for a median duration of 7 months; and early mortality was about 10%.

In the absence of two unfavorable features (ie, age greater than 50 years and extensive prior therapy for more than 12 months), recovery of granulocytes and platelets to safe levels exceeding 500/ μ L and 50,000/ μ L, respectively, occurred within 21 and 26 days after HDM. Appreciating the obvious limitations inherent in comparisons with historic controls, 24

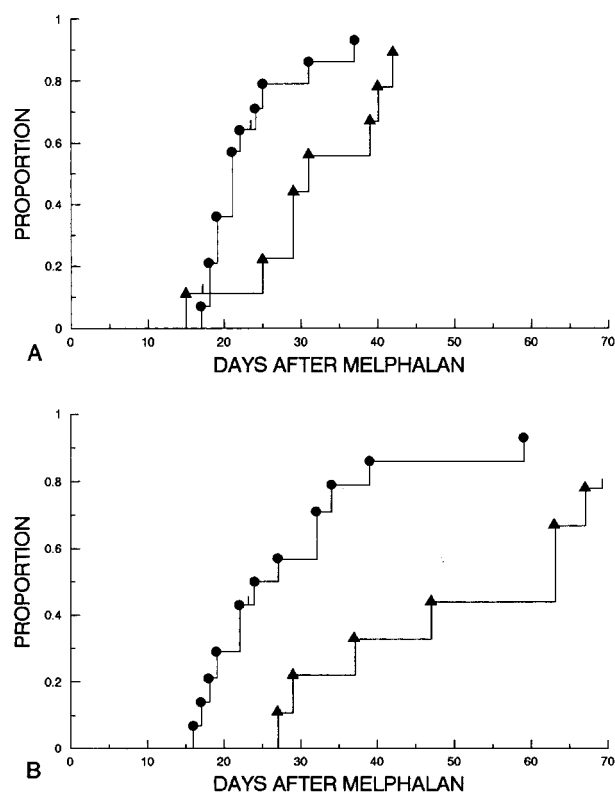


Fig 2. Faster granulocyte (A) and platelet recoveries (B) in patients ≤ 50 years and/or with ≤ 12 months of prior therapy ($n = 14$; $\bullet$) compared with those presenting with both adverse features ($n = 9$; $\blacktriangle$). A, $P = .03$; B, $P = .009$.

similar patients (among a larger group of 43) treated previously without GM-CSF required 2 additional weeks for granulocyte and 5 more days for platelet recovery to comparable levels. Thus GM-CSF seems to be useful mainly in hastening neutrophil recovery in younger individuals with adequate hematopoietic stem-cell reserve. In the absence of therapeutic benefit and with increased toxicity from higher doses, especially among older patients, the generally well-tolerated low GM-CSF dose of 0.25 mg/m² is recommended for use in conjunction with HDM.

The question arises where, in the overall management of myeloma, HDM and GM-CSF should be used. Since GM-CSF affords shortening of potentially fatal marrow aplasia mainly in younger patients with shorter prior treatment history, this approach should be considered as salvage therapy early on when it is clear that VAD is ineffective in newly diagnosed or refractory myeloma. HDM is especially attractive because its efficacy extends to the presence of hypodiploidy and low plasma-cell RNA content, both of which are frequently associated with primary drug resistance.⁸ While superior to melphalan doses of 100 mg/m², marrow-ablative treatment with even higher doses of up to 200 mg/m² or combined with total body irradiation does not result in a high frequency of durable complete remissions even when applied as consolidation treatment after VAD or similar induction therapy.^{1,14,15} In the absence of an apparent

adverse effect on remission and survival times of up to 30% plasma cells in autografts, advances can be expected from more marked tumor cyto-reduction prior to marrow-supported high-dose therapy, employing truly non-cross-resistant regimens such as VAD, HDM with GM-CSF, and a recently reported regimen combining etoposide, dexamethasone, Ara-C, and cis-platinum (EDAP).¹⁶

Compared with other cytotoxic agents, melphalan seems to exert damage toward early hematopoietic progenitor cells, where a benefit from GM-CSF was perhaps not expected because of its presumed effect on more mature progeny.¹⁷ A recent experimental trial with marrow-ablative total body irradiation in monkeys, however, demonstrated complete hematologic recovery with G-CSF without hematopoietic stem-cell support, suggesting therefore a stimulatory effect of G-CSF (and perhaps of GM-CSF) on an early progenitor compartment.¹⁸ While recently identified as a potential myeloma growth factor in vitro together with interleukin-6 (IL-6),¹⁹ GM-CSF administered after HDM did not increase, even transiently, marrow plasmacytosis or myeloma protein concentrations monitored at weekly intervals. As the toxicities of other hematopoietic growth factors, such as interleukin-3 or interleukin-1 are being defined, combinations of such growth factors may complement and eventually perhaps replace hematopoietic stem cells as a means of supporting marrow-ablative cytotoxic therapy.

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