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Dose-intensive melphalan with stem cell support (CM regimen) is effective and well tolerated in elderly myeloma patients

ANTONIO PALUMBO, SABRINA TRIOLO, LUCA BALDINI*, VINCENZO CALLEA*, ANTONIO CAPALDI*, VALERIO DE STEFANO*, MARIELLA GRASSO*, MARINA LIBERATI*, CLAUDIO LOTESORIERE*, RAIMONDO MARCENÒ*, FILIPPO MARMONT*, PELLEGRINO MUSTO*, MARIA TERESA PETRUCCI*, MAURO SPRIANO*, ALESSANDRO PILERI, MARIO BOCCADORO

*Divisione di Ematologia dell'Università di Torino – Azienda Ospedaliera S. Giovanni Battista, Turin, Italy, and *Italian Multiple Myeloma Study Group*

ABSTRACT

Background and Objectives. **Multiple myeloma (MM) typically afflicts elderly patients. High-dose therapy has recently been shown to lead to a better outcome than standard treatment, mainly in younger patients. The extent to which older subjects can benefit from intensified approaches without excessive toxicity is examined in this study.**

Design and Methods. **Between December 1994 and May 1997, 12 *Italian Multiple Myeloma Study Group* institutions entered 68 patients at diagnosis (median age 65) into an intensified chemotherapy regimen: cyclophosphamide (CY) 3 g/m² plus melphalan 60 mg/m² followed by peripheral blood progenitor cells (PBPC) and G-CSF (CM regimen). CY (day 0) and G-CSF were used to mobilize PBPC harvested by a single leukapheresis on day 10. Melphalan was infused on day 11. PBPC were kept unprocessed at 4°C for 48 hours and reinfused on day 12. Three CM regimens were delivered at 6-month intervals.**

Results. **Sufficient PBPC to support the first CM cycle were available (median CD34⁺ harvest: 4.9×10^6/kg), but dropped significantly after the second (median CD34⁺ harvest: 2×10^6/kg) and the third (median CD34⁺ harvest: 0.9×10^6/kg). The median durations of severe neutropenia (absolute neutrophil count < 500 µL) were 3, 4, and 3 days, and those of severe thrombocytopenia (platelets < 25,000/µL) were 2.5, 2, and 1 days, after the first, second and third courses, respectively. The frequency of extramedullary toxicities was low. Treatment-related mortality (TRM) was 3% after the first CM, only. Complete remission (CR) was 14% after the first, 16% after the second and 27% after the third CM. After a median follow-up of 34 months (range 19-49 months), median event-free survival was 35.6 months.**

Interpretation and Conclusions. **These results indicate that dose-intensity of melphalan can be increased by reinfusing PBPC with acceptable low toxicity. The combination of CY and melphalan followed by PBPC is an effective chemotherapy for elderly myeloma patients. Repeated melphalan infusion hampered subsequent CD34⁺ harvests.**

Key words: myeloma, dose-intensive chemotherapy, melphalan, transplantation

Correspondence: Mario Boccadoro, M.D., Divisione di Ematologia dell'Università di Torino, Ospedale Molinette, via Genova 3, 10126 Turin, Italy. Phone: international +39-011-6635814 – Fax: international +39-011-6963737 – E-mail: mario.boccadoro@unito.it

Hematopoietic stem cell supported high-dose chemotherapy has recently become the treatment of choice for symptomatic patients with multiple myeloma (MM). Standard melphalan-prednisone (MP) is followed by no more than 5% CR and a median survival of no more than 3 years.[1] High-dose therapy (HDT) with melphalan greatly increases the CR rate up to 50%.[2] Attainment of CR has become a primary objective as a potential prelude to long term disease control.[2-7]

Since the introduction of autotransplantation, patients have usually been eligible for HDT up to the age of 60-65 years. The risk of serious complications limits this approach to patients younger than 60 with good performance status.[8-10] Intention to treat is 82% for myeloma patients under 60, but drops to 56% for those over 60.[9] Older patients represent more than 50% of the total. In a recent report, HDT was delivered to 49 patients aged > 65 years, and their outcome was compared to that of younger patients. Hematologic and extramedullary toxicities were comparable. Treatment related mortality (TRM) was slightly increased in older patients (8% versus 2%), and no differences in outcome were encountered.[11] We believe that the development of new dose-intensive chemotherapies with lower melphalan doses and possibly lower toxicity specifically designed for elderly patients is essential. In a pilot study, we evaluated the toxicity and efficacy of repeated 60 mg/m² melphalan doses delivered to patients with with refractory disease and a median age of 63 years.[12] This approach was well tolerated and improved the response rate and outcome compared with conventional chemotherapy. Here we evaluated the toxicity and efficacy of cyclophosphamide-melphalan (CM) regimen in myeloma patients treated at diagnosis in a multi-center trial. Simplification of the procedure and low morbidity allowed its use on an outpatient basis and in patients up to age of 70. The CM regimen was effective and health-care support was similar to that required for conventional chemotherapy.

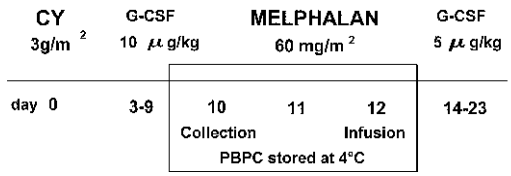

Figure 1. CM regimen: treatment plan. Cyclophosphamide (CY) and G-CSF were used to mobilize PBPC harvested by a single leukapheresis on day 10; melphalan was infused on day 11; PBPC were kept unprocessed at 4°C for 48 hours and reinfused on day 12.

Design and Methods

Patients

From December 1994 to May 1997, 12 Italian Multiple Myeloma Study Group institutions entered 68 myeloma patients at diagnosis into the study. The SWOG diagnostic criteria[13] and Durie and Salmon staging system were used.[14] Inclusion criteria were: age > 55 and < 70 years, normal cardiac, renal, pulmonary and liver function on the basis of routine clinical and laboratory examinations, echocardiography and lung-function tests. Patients with HBV, HCV, or HIV positivity were excluded. The institutional review board approved the protocol and written informed consent was obtained from all patients. The patients' characteristics are listed in Table 1.

Treatment regimen

CM regimen

Sixty-eight patients received 3 DAV debulking courses (dexamethasone - doxorubicin [adriamycin]-vincristine; adriamycin 50 mg/m^2 day 1, vincristine 1 mg day 1, dexamethasone 40 mg days 1, 2, 3, 4, at 28 day intervals). Four patients were excluded because of extrahematologic toxicity. The CM regimen (Figure 1) was, therefore, started in 64 patients. CY 3 g/m^2 was given on day 0 in 2 doses with subsequent i.v. MESNA 3 g/m^2 in 5 divided doses. Urine was monitored closely to detect hemoglobinuria on days 0-3. The infusions were performed on an outpatient basis. G-CSF was administered at 10 μg/kg/d s.c. from day 3 to 9. Blood counts were performed before CY and then every other day until harvest. The percentage of circulating CD34$^+$ cells was evaluated as previously described.[15,16]

On day 10 a single leukapheresis was performed and its product was kept at 4°C for 48 hours without further processing.

On day 11, melphalan 60 mg/m^2 was infused over 30 min. On day 12, PBPC were reinfused. G-CSF was administered at 5 μg/kg/d s.c. from day 14 to 23. If the number of CD34$^+$ harvested ranged from 0.5 to 1×10^6/kg or were < 0.5×10^6/kg, the doses of melphalan were decreased by 25% or 50% respectively. If the number of CD34$^+$ harvested was < 0.2×10^6/kg, melphalan was not administered. The CM regimen was repeated twice at 6 month intervals.

Supportive care

Patients received standard supportive care measures routinely used after conventional chemotherapy. Oral ciprofloxacin or cotrimoxazole was prescribed as antimicrobial prophylaxis. Patients who developed neutropenic pyrexia > 38°C received ceftriaxone at home. Patients with fever lasting longer than 24-48 hours after taking ceftriaxone were admitted for i.v. broad-spectrum antimicrobial therapy. Blood product support was used when the hemoglobin concentration dropped below 8 g/dL or the platelet count below 25,000/μL.

Response criteria and statistics

Partial response (PR) was defined as a 50% reduction of serum myeloma protein and 90% decrease of Bence Jones proteinuria. CR required disappearance of serum or urine myeloma protein analyzed by standard electrophoresis and marrow plasmacytosis < 1% for at least 2 months. All other results were regarded as failures. Statistical methods included chi-squared tests for comparison of rate[17] and Kaplan-Meier estimates.[18] Event-free and overall survival curves were plotted from the beginning of treatment.

Results

On an intention to treat basis, 52 % of patients completed the entire program. Sixty-three patients received the first course (1 was excluded because the CD34$^+$ harvest was < 0.2×10^6/kg), 49 the second course (6 were excluded because of relapse, 3 because the CD34$^+$ harvest was < 0.2×10^6/kg, 4 because of hematologic and extrahematologic toxicity, 1 because of a second neoplasm), and 34 the third course (8 were excluded because of relapse, 4 because CD34$^+$ harvest was < 0.2×10^6/kg, 3 because of hematologic and extrahematologic toxicity). The median number of CD34$^+$ cells reinfused was reduced from 4.9 to 2 to 0.9×10^6/kg during the first, second and third course, respectively. The distribution of CD34$^+$ harvest during each course is illustrated in Figure 2. According to the number of CD34$^+$ cells harvested, the doses of melphalan were decreased

Table 1. Patient characteristics.

	L-PAM 60 mg/m^2
No. of patients	73
Median age (range) (yrs)	65 (56-73)
	% of patients
*St*age at diagnosis	
II	36
III	64
Isotype	
IgG	63
IgA	32
Bence Jones protein	5
β_2-microglobulin >3 mg/L	28
Bone marrow plasmacytosis > 30%	80

Table 2. Toxicity after the first, second and third courses of the CM regimen.

	1st CM	2nd CM	3rd CM
	Median (range)		
No. of patients	63	53	51
CD34 harvested (1×10^6/kg)	4.9 (0.6-25)	2 (0.5-13)	0.9 (0.1-6)
Days with ANC < 500/uL	3 (1-9)	4 (2-7)	3 (1-4)
Days with platelets < 25,000/uL	2.5 (0-6)	2 (0-6)	1(0-7)
Number of RBC transfusions	1 (0-6)	0 (0-3)	0(0-0)
Number of platelet transfusions	1 (0-5)	0.5 (0-5)	1(0-3)
Days with fever > 38°C	0 (0-8)	0 (0-0)	0(0-0)
Days with antibiotic Use	0 (0-11)	0 (0-0)	0(0-0)
Days of hospitalization	0 (0-13)	0 (0-0)	0(0-0)
	%	%	%
Patients transfused with RBC	49	33	19
Patients transfused with platelets	41	28	15
Patients with fever >38°C	27	15	8
Patients hospitalized	21	8	4

ANC: absolute neutrophil count; RBC: red blood cells.

from 60 mg/m² to 45 mg/m² in 3% of patients after the first CM, 21% after the second and 38% after the third. The CM regimen was well tolerated. There were no complications of leukapheresis, apart from occasional lip paresthesia, caused by hypocalcemia and promptly abolished by i.v. calcium gluconate. Toxicity after CY was mild. The median absolute neutrophil count (ANC) before CY administration was 3,100/μL. The nadir was reached on day 7 or 8. A total of 57% of the patients showed thrombocytopenia < 100×10^9/L, the median value was 54×10^9/L. After CY, cases of extrahematologic toxicity were: 2 fevers of unknown origin, 2 gastrointestinal toxicities and 1 heart failure. Gross hematuria was never detected, despite the single-day infusion; 18% of patients experienced asymptomatic microscopic hematuria. The median duration of neutropenia and thrombocytopenia, transfusion requirement, incidence of fever and hospitalization were substantially unchanged from the first to the third course (Table 2).

Effect on neutropenia

After the first, second and third CM, median duration of severe neutropenia (ANC 500/μL) was 3, 4 and 3 days, respectively. Severe neutropenia lasting more than 7 days occurred in 15% of patients after the first course.

Effect on thrombocytopenia

After the first, second and third CM, median duration of severe thrombocytopenia (platelets < 25,000/μL) was 2.5, 2 and 1 day respectively. Dose-limiting thrombocytopenia, defined as more than 7 days with platelets < 25,000/μL, occurred in 7% of patients.

Transfusion requirement

The percentage of patients requiring red blood cell transfusion was 49% after the first course, 33% after the second and 19% after the third, while those requiring platelets ranged from 41% to 28% and to 15% (Table 2).

Extrahematologic toxicity

This was septic shock (1), pneumonia (2), fever of unknown origin (12), mucositis (8), gastrointestinal toxicity after the first course (1); fever of unknown origin (9), mucositis (5), gastrointestinal toxicity (1),

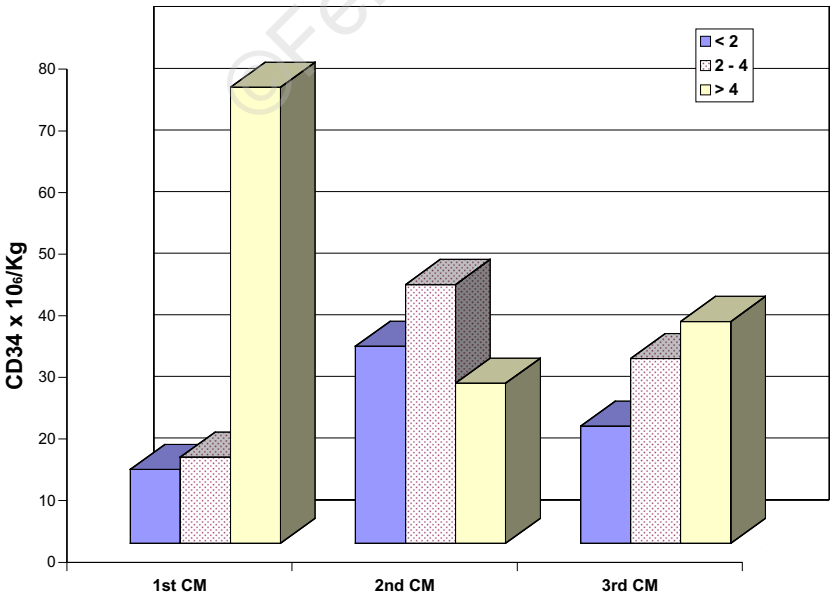

Figure 2. Distribution of patients harvesting < 2, 2-4, and > 4 CD34+ x 10^6/kg during 1st, 2nd and 3rd CM regimen.

heart failure after the second course (3); fever of unknown origin (5), mucositis after the third course (3). One septic shock and one pneumonia caused early death.

Using an intention to treat approach, the CM regimen induced 27% CR and 85% PR. After the first, second and third courses PR were 78%, 82% and 85%, and CR were 14%, 16% and 27%, respectively (Table 3).

After a median follow-up of 34 months (range 19-49), median event-free survival was 35.6 months (Figure 3). Median overall survival was not reached.

Discussion

Cytokines and stem cell support allow significant chemotherapy dose intensification. Hematopoietic growth factors improve neutropenia.[16] Peripheral blood progenitor cells induce faster neutrophil and platelet recovery, and reduce blood product support and therapy-related morbidity.[10,19-21]

PBPC mobilized by a chemotherapy rebound and G-CSF can be harvested at an outpatient blood bank. A single leukapheresis may be sufficient to support an intensified regimen. CY 1.2 g/m^2 efficiently mobilizes stem cells and increasing doses proportionally enhance the number.[12] We have previously reported that CY 3 g/m^2 has negligible toxicity in an outpatient setting, while yielding an adequate CD34 cell harvest.[12] In a recent study, mobilization with G-CSF alone was compared with CY 6 g/m^2 plus G-CSF: higher morbidity, greater CD34 cell mobilization, but comparable hematopoietic recovery after transplantation were observed.[23]

PBPC were stored for 48 hours at 4°C. The possibility of longer storage at 4°C has been evaluated.[12,24] Significant CFU-GM progenitor loss appeared after 72 hours at 4°C (10-50%), but 5-15% loss has been observed after 48 hours at 4°C. Freeze-thawing kills at least 20-30% of colony-forming cells.[25] Storage at 4°C for 48 hours is generally available.[26] It is inexpensive, does not require specific equipment and specialized staff, and is at least equivalent to cryopreservation in terms of viability.

Our single leukapheresis approach allowed a median harvest of 4.9×10^6/kg CD34$^+$ cells after the first CM but dropped to 2 after the second and to 0.9 after the third. Therefore, harvests were excellent after the first CM, then dropped significantly and only 52% of patients could receive the third CM course. Since intermediate doses of melphalan hampered subsequent PBPC recovery, in a more recent trial, CY 4 g/m^2 and G-CSF were used to mobilize at the beginning of treatment. Multiple leukaphereses were performed to optimise and increase PBPC harvest. After two or three leukaphereses, 90% of patients mobilized at least 6×10^6/kg CD34. These numbers were adequate to support three courses of melphalan 100 mg/m^2 in 94% of patients.[27]

Table 3. Clinical response.

	1stCM (%)	*2ndCM (%)*	*3rdCM (%)*
No response	22	18	15
Partial response*	78	82	85
Complete remission*	14	16	27

**See text for definition.*

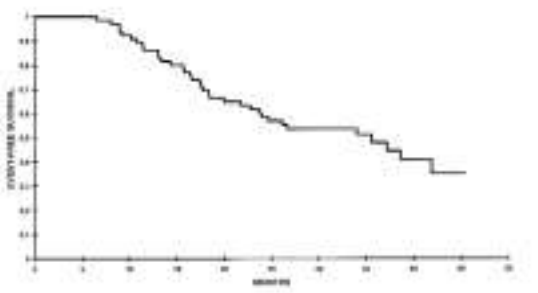

Figure 3. Event-free survival of myeloma patients treated with the CM regimen.

In a previous report we showed that using PBPC the dose intensity of melphalan could be doubled without any change in hematologic toxicity.[12] The duration of neutropenia and thrombocytopenia was identical when the CM regimen (CY 3 g/m^2 and melphalan 60 mg/m^2) was compared with melphalan 30 mg/m^2, and halved when the CM regimen was compared with melphalan 60 mg/m^2. In the CM regimen, melphalan is administered when hematopoietic cells are actively proliferating due to G-CSF stimulation. This could result in a higher hematologic toxicity compared to that produced by the same dose administered in a steady-state period. Apparently this was not the case, and a prompt recovery was observed with PBPC support. However, neoplastic plasma cells are also recruited into the cell cycle: this was reported several years ago and is the basis for the time sequential chemotherapy regimens proposed for myeloma and leukemia.[28-30] It could also explain the high response rate observed in the sequential CM protocol with a relatively low dose of melphalan.

Encouraging results with high-dose melphalan followed by stem cell support have been reported in selected series of myeloma patients.[12, 31-34] In a randomized study by Attal *et al.*, HDT was superior to standard treatment[32] as it was in a retrospective case-matched study by the SWOG.[31] In refractory patients, melphalan 60 mg/m^2 produced a better response rate and outcome than 30 mg/m^2.[22] Results obtained in this pilot study on refractory patients were confirmed by the present analysis in which patients at diagnosis received the same CM regimen in a multicenter trial. In another pilot study, 71 myeloma patients were treated at diagnosis with two or three courses of melphalan at 100 mg/m^2 (MEL100). Clinical outcome was compared to 71 pair mates selected from patients treated at diagnosis with MP and matched for age and β_2-microglobulin. CR was 47% after MEL100 and 5% after MP. Median event-free

survival was 34 months for MEL100 patients and 17 months for MP.[27] Altogether these different trials demonstrate that intermediate dose melphalan has a tremendous impact on clinical outcome. Since the development of the MP regimen in 1969[35] several combination chemotherapy trials have failed to demonstrate a clinical advantage over MP. Recently, HDT and now intermediate dose melphalan have significantly improved clinical outcome. The key unsolved issue remains the comparison between high-dose regimens and intermediate dose melphalan for elderly myeloma patients in terms of toxicity, response rate and survival.

Comparison of the CM regimen with other high-dose regimens is difficult because of the heterogeneity of induction as well as response requirements before transplant. Cunningham reported on patients receiving melphalan at 200 mg/m^2 (MEL200) who experienced 2% TRM, 75% CR and a median event-free survival of 2.0 years.[36] Powles *et al.* reported on 195 patients receiving MEL200 with 53% CR and event-free survival of 2 years.[37] Fermand *et al*.[38] observed 11% of TRM, 20% CR and event-free survival of 3.6 years. Harousseau treated 133 patients with melphalan at 140 mg/m^2 plus TBI and noted 4% TRM, 37% CR and event-free survival of 2 years.[39] Barlogie *et al.* reported on 231 patients receiving MEL200 with 41% CR, TRM 5% and event-free survival of 3.6 years.[40] Palumbo *et al.* described 71 patients receiving MEL100 with 0% of TRM, 47% of CR and event-free survival of 3 years.[27] Here we show a 3% TRM, 27% CR and event-free survival of 3 years. Despite the great heterogeneity of treatment approaches and patient enrollment these data suggest that a similar outcome can be achieved with a less intensive regimen. Whether or not intermediate dose melphalan is as effective as high-dose melphalan remains an open question.

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Contributions and Acknowledgments

APa conceived the study, contributed to data analysis and wrote the article; ST was responsible for data collection, interpretation and paper writing; LB, VC, AC, VDS, MG, ML, CL, RM, FM, PM, MTP, MS followed-up patients, performed the data analysis and contributed to the interpretation of the data; MB conceived and coordinated the study, his critical review was of invaluable help; APi contributed to the study design, data analysis and gave his final approval to the manuscript. All the authors revised the paper. The order of the authors reflects their contribution to this study in their own center, except for MB and APi who are the heads of the department in which the major part of the study was performed.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- Intermediate dose melphalan followed by stem cell reinfusion can be delivered to elderly myeloma patients (median age 65 years) with low toxicity.
- CY 3 g/m^2 + melphalan 60 mg/m^2 increase the proportion of myeloma patients achieving CR.[41]

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