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


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ABSTRACT

Background and Objectives. Multiple myeloma (MM) typically affects 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 x 10⁶/kg), but dropped significantly after the second (median CD34+ harvest: 2 x 10⁶/kg) and the third (median CD34+ harvest: 0.9 x 10⁶/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 extra-medullary 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.

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

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 and Durie and Salmon staging system were used. 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/m² 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/m² was given on day 0 in 2 doses with subsequent i.v. MESNA 3 g/m² 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. On day 10 a single leukapheresis was performed and its product was kept unprocessed at 4°C for 48 hours and reinfused on day 12.

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 and Kaplan-Meier estimates. 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 × 10⁶/kg), 49 the second course (6 were excluded because of relapse, 3 because the CD34+ harvest was <0.2 × 10⁶/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+ cells reinfused was reduced from 4.9 to 2 to 0.9 × 10⁶/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 was decreased as indicated in Table 1.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>L-PAM 60 mg/m²</th>
<th>No. of patients</th>
<th>Median age (range) (yrs)</th>
<th>% of patients</th>
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<tr>
<td></td>
<td>73</td>
<td>65 (56-73)</td>
<td>64</td>
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<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
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<th>III</th>
</tr>
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<tbody>
<tr>
<td>% of patients</td>
<td>36</td>
<td>64</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Isotype</th>
<th>IgG</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td>63</td>
<td>32</td>
</tr>
</tbody>
</table>

| Bone marrow plasmacytosis > 30% | 80 |

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.
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 × 10⁹/L, the median value was 54 × 10⁹/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),...
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. Peripheral blood progenitor cells induce faster neutrophil and platelet recovery, and reduce blood product support and therapy-related morbidity.

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/m² efficiently mobilizes stem cells and increasing doses proportionally enhance the number. We have previously reported that CY 3 g/m² has negligible toxicity in an outpatient setting, while yielding an adequate CD34 cell harvest. In a recent study, mobilization with G-CSF alone was compared with CY 6 g/m² plus G-CSF: higher morbidity, greater CD34 cell mobilization, but comparable hematopoietic recovery after transplantation were observed.

PBPC were stored for 48 hours at 4°C. The possibility of longer storage at 4°C has been evaluated. 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. Storage at 4°C for 48 hours is generally available. 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 x 10⁶/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/m² and G-CSF were used to mobilize at the beginning of treatment. Multiple leukaphereses were performed to optimize and increase PBPC harvest. After two or three leukaphereses, 90% of patients mobilized at least 6 x 10⁶/kg CD34. These numbers were adequate to support three courses of melphalan 100 mg/m² in 94% of patients.

In a previous report we showed that using PBPC the dose intensity of melphalan could be doubled without any change in hematologic toxicity. The duration of neutropenia and thrombocytopenia was identical when the CM regimen (CY 3 g/m² and melphalan 60 mg/m²) was compared with melphalan 30 mg/m², and halved when the CM regimen was compared with melphalan 60 mg/m². 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. 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. In a randomized study by Attal et al., HDT was superior to standard treatment as it was in a retrospective case-matched study by the SWOG. In refractory patients, melphalan 60 mg/m² produced a better response rate and outcome than 30 mg/m². 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/m² (MEL100). Clinical outcome was compared to 71 pair mates selected from patients treated at diagnosis with MP and matched for age and β₂-microglobulin. CR was 47% after MEL100 and 5% after MP. Median event-free...
survival was 34 months for MEL100 patients and 17 months for M P.27 Altogether these different trials demonstrate that intermediate dose melphalan has a tremendous impact on clinical outcome. Since the development of the M P regimen in 196925 several combination chemotherapy trials have failed to demonstrate a clinical advantage over M P. 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/m² (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. observed 11% of TRM, 20% CR and event-free survival of 3.6 years. Harousseau treated 133 patients with melphalan at 140 mg/m² plus TBI and noted 4% TRM, 37% CR and event-free survival of 2 years.38 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.41 Here we show a 3% TRM, 27% CR and event-free survival of 3.6 years.40


