

## Low transplant-related mortality in older patients with hematologic malignancies undergoing autologous stem cell transplantation

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**Background and Objectives.** Patients over 60 years old are frequently excluded from autologous stem cell transplantation (ASCT) programs due to a traditionally high rate of transplant-related mortality (TRM). We evaluated the results of ASCT in a group of 49 patients  $\geq$  60 years of age [32 males, median age 63 years (range, 60 to 71)] autografted in our institution from January 1995 to December 2001.

**Design and Methods.** There were 27 patients with multiple myeloma, 13 with non-Hodgkin's lymphoma, 3 with acute myelogenous leukemia, 3 with chronic myelogenous leukemia and 3 with other hematologic malignancies. The Karnofsky score was  $\geq$  80% in 47 cases. The median time from diagnosis to ASCT was 12 months (range, 5 to 61). Twenty-four patients were autografted in an early disease phase and 25 (51%) in an advanced phase. Peripheral blood stem cells were used in 46 patients (94%), bone marrow in one (2%) and bone marrow plus peripheral blood in two (4%). Forty-one patients received chemotherapy-only conditioning regimens, while only 8 patients received total body irradiation.

**Results.** Engraftment occurred in all but one patient. The median times to achieve a sustained absolute neutrophil count  $> 0.5 \times 10^9/L$  and a sustained platelet count  $> 20 \times 10^9/L$  were 13 (range, 10 to 35) and 13 days (range, 8 to 62), respectively. The actuarial 2-year overall survival was 67% [95% confidence interval (CI), 52-82%]. Four patients died without progression due to central nervous system (CNS) hemorrhage ( $n = 1$ ), CNS toxicity ( $n = 1$ ), fungal infection ( $n = 1$ ) or toxoplasmosis ( $n = 1$ ). One hundred-day and 1-year actuarial TRM were 4% (95% CI, 1-16%) and 8% (95% CI, 3-21%), respectively.

**Interpretation and Conclusions.** ASCT is a feasible procedure in selected elderly patients, with apparently similar rates of engraftment and TRM to those reported for younger patients.

**Key words:** older patients, autologous stem cell transplantation, transplant-related mortality.

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High-dose therapy and autologous stem cell transplantation (ASCT) offers a potential cure for many patients with high-risk malignancies who would have a poor outcome with conventional-dose chemotherapy.<sup>1</sup> Although age is the major determinant of the outcome of allogeneic stem cell transplantation, less is known about the influence of this factor on the success of ASCT. Knowledge of the outcome of ASCT in patients older than 50 to 55 years of age is of relevance since diseases for which ASCT is applicable, such as acute myelogenous leukemia (AML),<sup>2</sup> non-Hodgkin's lymphoma (NHL),<sup>3,4</sup> and multiple myeloma (MM),<sup>5</sup> are more frequent in older patients.

Patients aged  $\geq$  60 years have been traditionally excluded from most transplant programs and from most published series of high-dose therapy. This has been largely because of the anticipated poor tolerance and high transplant-related mortality (TRM) in this subset of patients.<sup>6-9</sup> Nevertheless, recent data suggest that low TRM can be achieved in older patients using peripheral blood (PB) hematopoietic progenitors and excluding total body irradiation (TBI) from the conditioning regimen.<sup>10-14</sup>

In this report we analyzed the hematologic and extra-hematologic toxicities, as well as TRM and long-term outcome, in a group of 49 patients  $\geq$  60 years undergoing ASCT in our institution.

### Design and Methods

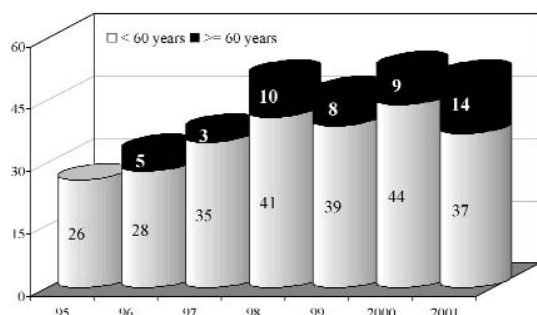
#### Characteristics of the patients

From January 1995 to December 2001, 273 consecutive patients, 173 males and 110 females with a median age of 49 (range, 17 to 71 years) were autografted in the Clinical Hematology Division of Hospital de la Santa Creu i Sant Pau. Forty-nine patients (18%) were  $\geq$  60 years of age and constitute the basis of this analysis (Figure 1). Patients were eligible for ASCT if the performance status as measured by the Karnofsky score was  $\geq$  80%, the left ventricular ejection fraction was  $> 50\%$ , forced expiratory volume in 1 second (FEV1) was  $> 50\%$ , diffusion capacity of the lung for carbon monoxide (DLCO) was  $> 50\%$  of the predicted value, and there was no major organ dysfunction not related to the underlying hematologic disorder. All patients gave written informed consent before undergoing ASCT.

The main characteristics of the patients are shown in Table 1. Twenty-seven patients (55%) were in an early phase of their disease and 22 patients (45%) were in an

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**Figure 1. Autologous stem cell transplantation in patients ≥ 60 years of age: experience of the Clinical Hematology Division, Hospital de la Santa Creu i Sant Pau from January 1995 to December 2001.**

advanced phase. For the purpose of this analysis, early phase was considered as acute leukemias or lymphoproliferative disorders in first complete remission (CR), CML in first chronic phase (CP) and MM autografted in CR or partial remission (PR) after first-line therapy. Advanced phase was considered as acute leukemias or lymphoproliferative disorders beyond first CR, CML in accelerated phase and MM undergoing ASCT in sensitive or resistant disease more than 12 months after diagnosis.

#### Source of hematopoietic progenitors and mobilization protocols

PB was the source of stem cells in 46 patients (94%). Two patients were autografted with both PB and bone marrow (BM) (4%) and one patient with BM alone (2%). BM was harvested under general anesthesia and cryopreserved following standard guidelines. In 12 patients autografted with PB±BM, hematopoietic progenitors were mobilized with granulocyte colony-stimulating factor (G-CSF) alone (doses ranging between 5 and 10 µg/kg/day sc). In the remaining 36 patients (74%), PB progenitor cells (PBPC) were collected after chemotherapy (cyclophosphamide 1.5 g/m<sup>2</sup> iv) plus G-CSF.

Large volume aphereses (≥ 15 liters) were performed in all cases using a CS3000 Plus (Fenwall, Baxter Healthcare, Deerfield, IL, USA) or a COBE SPECTRA (COBE, Lakewood, CO, USA) separator. Leukaphereses were started when the leukocyte counts in PB were ≥ 1.0×10<sup>9</sup>/L or the number of circulating CD34<sup>+</sup> cells in PB were ≥ 2.5×10<sup>3</sup>/mL. Aphereses were performed daily until a minimum of 2×10<sup>6</sup>/kg CD34<sup>+</sup> cells had been obtained.

**Table 1. Characteristics of the patients.**

Characteristics	N (%)
N. of patients	49 (100)
Sex	
Male	32 (65)
Female	17 (35)
Age, median (range) in years	63 (60 - 71)
Diagnosis	
MM	27 (56)
AML	3 (6)
CML	3 (6)
NHL	13 (26)
Others*	3 (6)
N. lines of therapy before ASCT	
1 line	37 (75)
≥ 2 lines	12 (25)
Diagnosis - ASCT, median (range) in months	12 (5 - 61)
Disease status at ASCT <sup>o</sup>	
Early phase	24 (49)
Advanced phase	25 (51)
Karnofsky status at ASCT ≥ 80%	47 (96)

MM: multiple myeloma; AML: acute myelogenous leukemia; CML: chronic myeloid leukemia; NHL: non-Hodgkin's lymphoma; ASCT: autologous stem cell transplantation.

\*Chronic lymphocytic leukemia (n = 1), Hodgkin's disease (n = 1), systemic amyloidosis (n = 1). <sup>o</sup>See text for definitions.

#### Conditioning regimens

Patients were conditioned according to their underlying disease and the different institutional protocols. Patients with MM received melphalan 140 mg/m<sup>2</sup> iv plus fractionated TBI (12 Gys) (n = 4), melphalan 200 mg/m<sup>2</sup> iv (divided over 2 days) (n = 11) or the combination of busulfan (12 mg/kg po, total dose with dose-adjusting depending on plasma busulfan levels) and melphalan 140 mg/m<sup>2</sup> iv (n = 12). Patients with myeloid malignancies (acute or chronic leukemias) received the combination of busulfan (16 mg/kg po, total dose) plus cyclophosphamide (120 mg/kg iv) (n = 2) or cyclophosphamide (120 mg/kg iv) plus hyperfractionated TBI (13.25 Gy) (n = 4). Patients with lymphoid malignancies received the BEAM protocol (BCNU 300 mg/m<sup>2</sup> iv × 1 day, etoposide 150 mg/m<sup>2</sup> iv × 4 days, cytarabine 200 mg/m<sup>2</sup> twice daily iv × 4 days and melphalan 140 mg/m<sup>2</sup> iv × 1 day (n = 14), or the CBV combination (cyclophosphamide 1.2 g/m<sup>2</sup> iv × 4 days, etoposide 200 mg/m<sup>2</sup> twice daily iv × 3 days and BCNU 300 mg/m<sup>2</sup> iv × 1 day) (n = 1). The patient with systemic amyloidosis was conditioned with melphalan 200 mg/m<sup>2</sup> iv (divided over 2 days).

**Table 2. Hematologic and extrahematologic toxicities after ASCT.**

Hematologic toxicity	
	Median (range) in days
Granulocyte count $>0.5 \times 10^9/L$	13 (10 - 35)
Platelets $>20 \times 10^9/L^*$	13 (8 - 62)
Platelets $>50 \times 10^9/L^*$	18 (12 - 179)
Hospitalization time	23.5 (16 - 48)

\*Evaluated in only 48 patients.

Extrahematologic toxicity	
Toxicity	Grade $\geq 2$ [Number (%)]
Mucositis <sup>^</sup>	38 (78)
Gastrointestinal tract <sup>^</sup>	21 (43)
Renal <sup>°</sup>	3 (6)
CNS <sup>*</sup>	2 (4)
Cardiac	3 (6)

\*CNS. Central nervous system. One patient died in deep coma on day +24.  
<sup>^</sup>Two patients required total parenteral nutrition. <sup>\*</sup>Namely nausea/vomiting and diarrhea. <sup>°</sup>One patient required hemodialysis treatment because of acute renal failure.

### Supportive therapy

All patients were cared for in private rooms with laminar air flow and nursed in reversed-barrier isolation. Oral acyclovir at doses of 800 mg q12h was initiated with the conditioning regimen and continued up to day +30. No antibiotic or antifungal prophylaxis was administered. Oral fluconazole (200 mg *po qd*) was empirically given when grade  $\geq 2$  mucositis developed. Broad-spectrum intravenous antibiotics were started when the patient developed neutropenic fever. Amphotericin B was added to broad-spectrum antibiotics after 5 to 7 days of neutropenic fever. *P. carinii* prophylaxis with oral trimethoprim/sulfamethoxazole was started on day +30 after hematologic recovery and given up to day +90. No prophylactic growth factors were administered after hematopoietic progenitor cell infusion. Packed red blood cells were transfused to maintain a hemoglobin level  $> 80$  g/L and prophylactic platelet units were given with platelet counts of  $< 20 \times 10^9/L$ . All transfused blood products were irradiated (20 Gy). Total parenteral nutrition was given in case of severe mucositis.

### Evaluation of toxicity and statistical methods

Granulocyte recovery was defined as the first day with a granulocyte count  $> 0.5 \times 10^9/L$  and platelet recovery as the first of three days with a self-sustained platelet count  $> 20 \times 10^9/L$ . Hospitalization time was calculated from the day of hematopoietic progenitor cell infusion to the day of hospital discharge. Transplant-related toxicity was evaluated according to Bearman's criteria.<sup>15</sup>

All patients were followed for at least 100 days. Four patients receiving a second transplantation (3 autologous and 1 allogeneic) were censored at the day of the second transplantation. Overall survival (OS) was computed from the day of transplant until death from any cause using the method of Kaplan and Meier.<sup>16</sup> TRM was defined as non-relapse or disease progression mortality and estimated using a cumulative incidence estimate.<sup>17</sup>

### Results

#### PBPC collection and infused cellularity

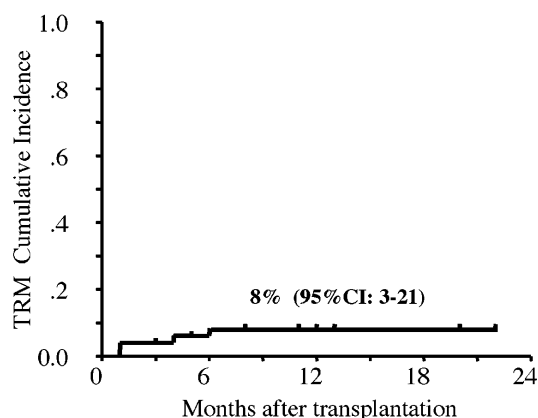
In the 46 (94%) patients autografted with PB only a median number of 1 (range, 1 to 6) apheresis was performed. In 8 patients (17% of the series) a second mobilization attempt was required to collect the target CD34<sup>+</sup> cell dose. A median number of 10.7 (range, 0.06 to 50.1)  $\times 10^8/kg$  mononuclear cells (MNC) and 3.7 (range, 2-12)  $\times 10^6/kg$  CD34<sup>+</sup> cells were infused. Two patients were autografted from both BM and PB; the BM cellularity collected was: 22.3  $\times 10^7/kg$  total nucleated cells (tNC) and 1.1  $\times 10^5/kg$  CFU-GM. In the one patient autografted from BM, the infused cellularity was 16.3  $\times 10^7/kg$  tNC and 0.36  $\times 10^5/kg$  CFU-GM.

#### Hematopoietic reconstitution and time to discharge

Engraftment was successful in all 49 patients except for one (2% of the series) who died on day +132 after ASCT due to a central nervous system hemorrhage without platelet recovery (infused cellularity was 16.3  $\times 10^7/kg$  tNC and 0.36  $\times 10^5/kg$  CFU-GM). Times to hematologic recovery and of hospitalization are shown for the remaining 48 patients in Table 2.

#### Transplant-related morbidity and mortality

Extrahematologic toxicity is described in Table 2. All patients developed neutropenic fever requiring broad-spectrum intravenous antibiotics. The median duration of fever was 7 days (range, 1-33). In 22 cases (45% of the series) blood cultures were negative while in 27 cases a clinical or microbiologically defined infection occurred. A catheter-related bacteremia was the single most common type of infection (n = 17). Only one patient developed

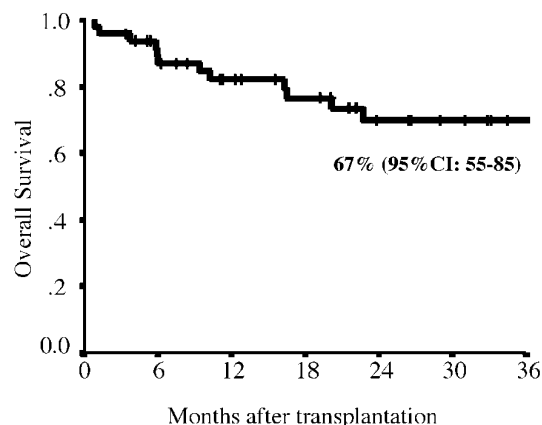


**Figure 2.** One-year transplant-related mortality cumulative incidence of the whole series.

*E. coli*-associated septic shock.

Cumulative TRM was 8% (95% CI, 3-21) at 1 year (Figure 2). There were two transplant-related deaths in the first 100 days after transplantation; 2 patients with MM (one in CR and the other in PR) died from multiorgan failure and grade 4 CNS toxicity and from a disseminated fungal infection on days +24 and +37 after ASCT, respectively. Two cases of TRM occurred beyond day +100; a patient with non-Hodgkin's lymphoma transplanted in partially-treated second relapse died on day +111 due to a CNS toxoplasmosis and a patient with acute myeloid leukemia in 1<sup>st</sup> CR died due to CNS hemorrhage with no signs of platelet recovery on day +179. There were no differences observed between patients transplanted in early or advanced phases with respect to 100-day and 1-year TRM [3.7% (95% CI, 0.5-25%) vs. 4.5% (95% CI, 0.7-30%) and 8% (95% CI 2-30%) vs. 9% (95% CI 2-35%), respectively]. The conditioning regimen did not influence the 1-year TRM: 10% (95% CI, 4-30%) for patients conditioned with chemotherapy ( $n = 29$ , 60% of the series), 12% (95% CI, 2-78%) for patients conditioned with TBI-containing protocols ( $n = 8$ , 16%) and 0% for patients receiving high-dose melphalan alone ( $n = 12$ , 24%). As shown, the TRM seemed somewhat lower for patients receiving high-dose melphalan.

The TRM in our series did not significantly differ from that observed in a group of 224 consecutive patients younger than 60 years autografted during the same period of time in our institution [3% (95% CI, 1-6%) at 100 days and 6% (95% CI, 3-10%) at 1 year].



**Figure 3.** Two-year actuarial overall survival of the whole series.

#### **Follow-up, response and overall survival**

The median follow-up of the whole series was 12 months (range, 1 to 51). The actuarial 2-year OS was 67% (95% CI, 52-82%) (Figure 3). At the time of last follow-up, 34 patients were alive, 26 in CR or stable disease and 8 in disease progression, while 15 patients had died, 4 due to TRM and 11 due to progressive disease.

#### **Discussion**

Age has generally been considered a limiting factor for high-dose chemo/radiotherapy and ASCT. In fact, most prospective studies performed in patients with hematologic malignancies exclude patients older than 60 years. Although the first published series reported a TRM as high as 25 to 35%, 6-8 more recent studies indicate that the TRM could be similar in older and in younger patients.<sup>10-14</sup> In our institution, inclusion of older patients in the autologous transplantation program has increased during the last years: autografts in patients  $\geq 60$  years represented less than 8% of the autografting activity up to 1997 while they represented almost one third of all the autografts performed in 2001 (Figure 1). The TRM reported here compares favorably with that reported by other authors from single institutions and by European Bone Marrow Transplantation Group.<sup>8</sup>

Several factors may explain the decrease in TRM during the most recent period. PB has almost completely replaced BM as the source of progenitor cells for autologous transplantation, leading to a

significant reduction in the aplastic phase after transplantation. This has translated into fewer severe infections and less bleeding, which were the major causes of TRM. As demonstrated in our study and by other groups<sup>11,13</sup> PBPC collection is feasible in older patients. In our series it was possible to collect sufficient numbers of PB stem cells from all but 3 patients, and hematologic recovery after ASCT was not significantly different from that observed in younger patients. In fact, the patient with acute myeloid leukemia in 1<sup>st</sup> CR, who died because of a CNS hemorrhage on day +179 after ASCT without signs of platelet recovery did not mobilize progenitor cells into PB and underwent a BM collection, which also had a low hematopoietic potential as demonstrated by the low numbers of CFU-GM.

Significant changes in conditioning protocols have also contributed to the decrease of TRM in older patients. TBI-based conditioning protocols as well as the combination of cyclophosphamide and busulfan are less frequent nowadays than they were 10 years ago. In some initial series,<sup>6</sup> TRM was in part due to toxicity from the preparative regimen (veno-occlusive disease of the liver and idiopathic pneumonia). The clearance of many drugs decreases with age<sup>18-20</sup> and this can lead to prolonged exposure to the conditioning and increased toxicity. The use of less toxic preparative protocols, e.g., the BEAM combination<sup>21</sup> or melphalan-200 should be pursued in the elderly population.

Multiple myeloma and NHL are the two diseases that affected the majority of patients in our study. The Arkansas group demonstrated that age was not a biologically adverse parameter for MM patients treated with high-dose melphalan in 49 patients aged  $\geq 65$  years who were compared with 49 younger pair mates from the same institution.<sup>22</sup> The same authors presented their results in a group of highly selected MM patients older than 70 years undergoing a tandem ASCT as front-line therapy or after first relapse.<sup>23</sup> Their results support the idea that ASCT with intermediate doses of melphalan (140 mg/m<sup>2</sup> iv) is not associated with a high TRM, that mobilization and collection of PBPC is feasible and that the intensity of the first conditioning regimen does not compromise the performance of a second ASCT. In our series we included 27 MM patients, of whom of over 50% were autografted in first response after front line chemotherapy. The conditioning regimen included melphalan alone or in combination with TBI or busulfan. Two patients who received the combination of melphalan and busulfan as conditioning regimen died, which gives an overall TRM in this group of 7.4%, not significantly different from that observed in other series.

Treatment of NHL in elderly patients remains a challenge. Although high-dose therapy and ASCT is potentially curative in some subgroups of patients, many physicians are reluctant to use this thera-

peutic approach because of a higher than expected procedure-related mortality. In fact, both the EBMT<sup>8</sup> and the Seattle analyses<sup>24</sup> reported a high TRM of 18% and 17% at 1 year, respectively. In our small series of 13 patients, only one patient died of transplant-related causes: this patient had been heavily-pretreated and autografted in second PR.

In conclusion, this report indicates that ASCT is a feasible procedure in patients older than 60 years, and has a TRM similar to that reported for younger patients. The mobilization procedure, the engraftment rate and the hematologic and extra-hematologic toxicities are also similar. The routine use of PBPC cells and of less toxic conditioning protocols may allow TRM to be reduced even further in this subgroup of patients.

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## Pre-publication Report & Outcomes of Peer Review

### Contributions

LV and AS designed the study and were responsible for collection and interpretation of the data and preparation of the manuscript. CC was involved in the statistical analysis and interpretation of the data. MAS, RM, DV, AA, JB, MG, and SB were involved in the clinical management of all the patients autografted in our Unit. JS led the project and had a major role in revising and preparing the final version of the manuscript.

### Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

### Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Guido Tricot, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Tricot and the Editors. Manuscript received September 4, 2002; accepted January 25, 2003.

In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes.

### What is already known on this topic

Patients over the age of 60 are commonly excluded from autologous stem cell transplantation programs because of a high rate of transplant-related mortality

### What this study adds

Findings of this study suggest that autologous stem cell transplantation is a feasible procedure in selected elderly patients. A good performance status before transplantation, the use of peripheral blood hematopoietic progenitors, and excluding total body irradiation from the conditioning regimen all appear to be factors associated with lower transplant-related mortality.

### Caveats

This is a retrospective study and, as such, involves intrinsic limitations. Future studies should more clearly define the criteria for deciding autologous stem cell transplantation in individual patients over 60 years old.