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Feasibility of a mixed inpatient-outpatient model of peripheral blood stem cell transplantation for multiple myeloma

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Background and Objectives. A progressively growing number of peripheral blood stem cell transplants (PBSCTs) are being performed in patients with newly diagnosed multiple myeloma (MM) since they are ever more frequently being offered as up-front therapy. Furthermore, there are considerable concerns regarding the appropriate use of health care resources in order to reduce costs associated with PBSCT. One of the strategies attempted to reach this goal is outpatient-based PBSCT.

Design and Methods. The aim of this study was to analyze the feasibility of a mixed inpatient-outpatient model (MIOM) for MM patients receiving high-dose melphalan, and homogeneously undergoing autologous PBSCT, antimicrobial and antiviral prophylaxis and post-transplant growth factor treatment. Furthermore, we retrospectively compared results of the MIOM with those of the traditional total inpatient model (TIM).

Results. MIOM was applied for 60 transplants in a total of 29 MM patients. Results were compared with retrospective data concerning the traditional TIM for 40 transplants (27 MM patients). MIOM cases were older than TIM ones (55.3±6.3 years vs 49.6±9.2 years, p=0.01), but were comparable for sex and disease status. Granulocyte recovery time was shorter in the MIOM group (9.0±0.7 vs 9.7±1.2 days, p=0.004), while a similar number of stem cells were infused. There was no difference in platelet engraftment. The number of episodes and duration of grade II-IV mucositis were similar in both groups. Fever occurred in fewer MIOM cases (25% v 51.6%, p=0.02), while its duration was similar. In multivariate analysis, mucositis (grades II-IV) was the sole independent predictor of fever development (p=0.002). Half of the MIOM cases never required re-admission, 26 were re-admitted (median hospital stay 9 days) and 4 cases were not discharged (median hospital stay 15 days). The median time to discharge of TIM cases was 20 days. Non-hematologic toxicities were low in both groups.

Interpretation and Conclusions. Since outpatient management and liberal hospitalization criteria have resulted in safe conduct of MIOM transplants, this program can be safely offered to MM patients.

Key words: multiple myeloma, stem cell transplant, outpatient.

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Multiple myeloma (MM) is a neoplastic disease of terminally differentiated B-cells with a progressive and ultimately fatal clinical course.[1] Despite the introduction of melphalan associated with prednisone, the outcome of MM patients has not significantly changed, and it remains questionable whether any of the other currently available standard combination regimens are more effective.[2] In this regard, a meta-analysis failed to prove that any combination of conventional chemotherapy produced any significant improvement in survival over that achieved by melphalan and prednisone.[3] Instead, the promising results obtained by high-dose chemotherapy with autologous stem cell rescue have led to its increasingly widespread use in patients affected by MM.[4,5,6] That the choice of this therapeutic approach is unquestionably preferable for MM patients is supported by results of a randomized trial, which definitively showed the superiority of high-dose over conventional treatment in terms of response rate, event-free and overall survival.[7] A further step towards standardization of stem cell transplantation in MM was concern about the conditioning regimen. In this regard, the Intergroupe

Francophone du Myélome randomized trial concluded that high-dose melphalan (HDM) at 200 mg/m^2 is less toxic than and at least as effective as HDM 140 mg/m^2 plus 8 Gy total body irradiation and has, therefore, become the new standard conditioning regimen for peripheral blood stem cell transplantation in MM patients.[8] Finally, Barlogie *et al*. designed a trial to test whether a *tandem* transplantation could induce a higher response rate and better long-term disease control,[9] though results of all ongoing randomized trials are still too immature to provide a definite conclusion on the benefit for patients.[10-13]

The general concept that peripheral blood should replace bone marrow as the source of stem cells to rescue myeloablative regimens can also be extended to MM patients.[14] Both single and tandem high-dose therapy with PBSC appeared to be superior than bone marrow stem cell rescue in terms of response rate, event-free and overall survival.[10]

Based on the above mentioned clinical research data, PBSCT is being systematically offered as up-front therapy to newly diagnosed MM patients in our institution, leading to a progressively growing number of transplants. Traditionally, MM patients undergoing PBSCT are admitted to intensive care units in a total inpatient program (TIM) from the start of administration of the high-dose chemotherapy in order to receive hydration, antiemetic therapy and support for the aplastic phase with prolonged hospital stays.

Recently, there has been considerable concern regarding the appropriate use of health care resources and attempts have been made to reduce costs associated with PBSCT. One of the strategies used to reach this goal is outpatient-based PBSCT, which depends on the reduction of complications that necessitate hospitalization.[15] Accelerated neutrophil recovery consequent to the use of PBSC[16] and in response to post-transplantation administration of granulocyte colony-stimulating factors (G-CSF),[17] the improvement of oral antibiotic prophylaxis[18,19] and once daily dosing parental antibiotics[20] have clearly simplified the management of infectious complications, which represent the major cause of morbidity in patients undergoing PBSCT.

According to the Italian diagnosis-related group (DRG) system (*Ministry Decree, April 15, 1994, May 10th, 1994 Gazzetta Ufficiale n. 107*), to guarantee reimbursement for the costs of PBSCT, it is convenient to have the patient hospitalized for at least two nights. The aim of this study was to analyze the feasibility of a mixed inpatient-outpatient model (MIOM) for MM patients receiving high-dose melphalan, homogeneously undergoing PBSCT autografting, antimicrobial and antiviral prophylaxis, and post-transplant G-CSF treatment. Furthermore, we retrospectively compared results of the MIOM with those of the traditional TIM applied in our Center.

Design and Methods

Patients

All patients consecutively entering the MIOM program from January 1998 until September 2001 were included in the study. All TIM group clinical and hematologic data from October 1994 until the end date of the study were retrospectively collected. Table 1 shows the main clinical-hematologic data of the MM patients who entered this study. Of 56 MM patients undergoing PBSCT, 35 cases received a second and 9 a third PBSCT, for a total of 100 PBSCTs. Previous therapies mainly consisted of a modified VAD regimen (41 patients, 24 in the MIOM group), while 15 patients (5 in the MIOM group) received other chemotherapeutic approaches. No difference was demonstrated between the two groups in terms of sex, while a higher number of young patients was found in the TIM group.

Stem cell mobilization

Stem cells were mainly collected after cyclophosphamide mobilization at dosages ranging from 3.5 to 7 g/m^2 in 34 cases and the VAD regimen in 7 cases, associated with G-CSF 5 mg/kg (Table 1). Considering the target number of 2 or 3 PBSCT, we collected >20×10^6/kg stem cells. The 9 patients who failed to yield an adequate amount of stem cells (8 belonging to the MIOM group) received second mobilization therapy consisting of either G-CSF 10 mg/kg alone (2 cases) or the growth factor associated with cyclophosphamide in 4 cases, VAD regimen in 1 case and VP-16 2 g/m^2 in 2 cases.

Models of inpatient and of outpatient care

In 1994, TIM was the initial approach for the organization of PBSCT in MM patients in our institution. In this case, central venous catheter (CVC) insertion (day –5), fluid infusion (from day –4), high-dose chemotherapy administration (day –3), rest (days –2 to -1), PBSC infusion (day 0) and supportive care management (from day 1 to engraftment) were carried out in a positive-pressure reverse isolation room. After an accurate analysis of examples of outpatient care described in literature,[21] we designed our MIOM, operative since 1998. In this program, CVC insertion, fluid infusion, high-dose chemotherapy, together with supportive care of the aplastic phase, were carried out in an outpatient bone marrow transplant clinic. Patients were admitted to the

Table 1. Comparison of the main clinico-hematologic features of multiple myeloma patients undergoing peripheral blood stem cell transplantation (PBSCT) according to a mixed inpatient / outpatient model (MIOM) and a total inpatient model (TIM).

Variables	*MIOM*	*TIM*	*p*
Total number of patients	29	27	
Number of patients undergoing			
Single PBSCT	5	16	
Double PBSCT	17	9	ns
Triple PBSCT	7	2	
Total number of PBSCT	60	40	
Sex			
Male	19	18	ns
Female	10	9	
Age, mean±sd	55.3±6.3	49.6±9.2	0.01
Pre-PBSCT therapy			
VAD plus CTX	19	15	
VAD	5	2	ns
Others	5	10	
Stem cell collection after			
CTX	18	20	
VAD	5	3	ns
Others	6	4	
Number of aphereses			
One	1	3	
Two	7	9	
Three	9	9	ns
Four	7	2	
Five	2	1	
Six	3	2	
Seven	0	1	

inpatient unit for PBSC infusion on day 0 for 2 days only to guarantee maximum reimbursements according to the Italian DRG system. A prerequisite for the care of the MIOM patients was the availability of dedicated specialized staff and of an equipped facility operating 12 hours/day and during week-ends. Patients whose travel time to hospital exceeded 45 minutes were temporarily provided with free-of-charge suites equipped with emergency phone and a teleconference system (TELCAL project) by the *Associazione Italiana contro le Leucemie* local nearby housing project (CASAIL). Forty-nine transplants were performed in the MIOM program thanks to CASAIL lodging facilities.

MIOM candidates and selection criteria

To determine candidacy for the MIOM program, patients were screened both for the same eligibility criteria to undergo the TIM program, i.e. assessment of organ function and performance status, and for the following specific eligibility criteria: i) psychosocial evaluation to establish skills and compliance of patients and caregivers; ii) availability of a caregiver on a 24-hour basis; iii) housing in close proximity to the transplant center (i.e, less than 45 minutes driving distance); iv) competency and commitment of patients and caregivers, judged by an educational session; and v) signed and informed consent.

High-dose chemotherapy

Sixty PBSCTs were performed in the outpatient and 40 in the inpatient setting. Table 1 shows the number of single, double and triple PBSCTs carried out in both situations. In all cases, HDM 200 mg/m^2, administered in 3 doses on day -2, was employed as the conditioning regimen.

Prophylaxis

During the aplastic phase, TIM patients were admitted to a positive-pressure reverse isolation room. All patients received prophylaxis including oral ciprofloxacin (500 mg every 12 hours), acyclovir (800 mg every 8 hours), either fluconazole (300 mg/day) or itraconazole (200 mg/day) orally from day –5 until neutrophil recovery and trimethoprim/sulphomethaxazole from day –8 to day 0. All patients received DMSO-depleted apheretic products in order to drastically reduce nausea, vomiting and cardiovascular symptoms[22] and G-CSF at a dose of 5 mg/kg/day starting from 72 h after stem cell infusion until neutrophil engraftment.

Microbiological investigations, antimicrobial and supportive therapy

Clinical examinations were performed once daily and body temperature was measured at least three times a day for both MIOM and TIM patients. A febrile episode was defined as an axillary temperature exceeding >38°C on at least two consecutive occasions, in the absence of an obvious non-infectious cause of fever, such as transfusion of blood products or administration of cytotoxic drugs. When body temperature exceeded 38°C, blood and catheter cultures were set up. Furthermore, a chest X-ray examination was carried out in febrile patients. Empiric antibiotic therapy was started immediately after the temperature rose above 38°C. In both groups, packed red blood cell and platelet transfusions were given with hemoglobin <8 mg/dL and platelets count <10×10^9/L, respectively. All blood components were irradiated (1.5-2.0 Gy) and filtered before infusion. About half of the patients in the MIOM group received subcutaneous rHu-Epo 10,000 IU daily for 3 weeks after peripheral blood stem cell collection and stopped the day before the administration of chemotherapy with melphalan. An

oral daily dose of 200 mg of elementary iron was recommended to maintain appropriate iron availability and iron stores.

Criteria for hospital readmission for MIOM patients

Indications for readmission or no discharge after stem cell infusion included uncontrolled nausea, vomiting and/or diarrhea, severe mucositis requiring continuous fluid replacement, parental alimentation or narcotic drug use, pneumonia, cardiac and/or respiratory distress, fever unresponsive to first-line antibiotic therapy and any other toxicity judged unmanageable at home by medical staff. Finally, patients were also admitted at their own request.

Statistical methods

Clinical charts were examined by the authors. Data were analyzed by descriptive statistical methods and differences between groups were calculated using Fisher's exact test. Factors affecting fever development were investigated using logistic multivariate analysis.

Results

Engraftment

Forty cases followed a classical inpatient (TIM) program and 60 followed a mixed inpatient-outpatient (MIOM) model. All patients received high dose melphalan as conditioning regimen, PBSC autografting as the source of stem cells, equal antimicrobial and antiviral prophylaxis, and post-transplant G-CSF. Most outpatient cases have been transplanted in the last 2 years (Table 2). The number of $CD34^+$ cells infused was 5.8±4.4 s.d × 10^6/kg and 60% of MIOM cases were transplanted with >5×10^6 $CD34^+$ cells/kg, with no statistical difference between the TIM and MIOM groups (Table 2). In particular, only one TIM case received <3×10^6/kg stem cells, while 11/40 TIM and 24/60 MIOM cases were transplanted with >3 and <5×10^6 $CD34^+$ cells/kg. All patients became neutropenic after high-dose melphalan. MIOM patients had a significantly shorter time to engraftment (100 and 500 granulocytes/μL) and a shorter duration of severe neutropenia (Table 2). Just before PBSCT, platelet count exceeded 100×10^9/L in all but one patient, who presented with severe thrombocytopenia. The median time to >30, 50 and 100×10^9/L platelets was respectively 14, 17 and 19 days, with no difference between cases transplanted as an outpatient or as an inpatient. Finally, no intergroup differences in hematologic engraftment kinetics were observed between the first, second and third PBSCT (*data not shown*).

Table 2. Comparison of transplant characteristics for patients entering the TIM and MIOM programs.

Variables	*MIOM*	*TIM*	*p*
N° of transplants performed in:			
1994	0	1	
1996	0	1	
1997	0	9	
1998	1	7	
1999	6	7	
2000	27	7	
2001	26	9	
Stem cell support 10^6 $CD34^+$ cells/kg mean value ± sd	5.3±2.2	6.4±6.3	ns
N° of cases transplanted with $CD34^+$ cells ×10^6 /kg			
< 3	0	1	ns
≥ 3 < 5	24	11	
≥ 5 < 6	24	12	
> 6	12	16	
Days to neutrophils (mean value±sd)			
>100/μL	9.0 ±0.7	9.7±1.2	0.004
>500/μL	9.8 ±0.9	10.5±1.1	0.008
Days with neutrophils (mean value±sd)			
<100/μL	3.3±1.7	4.4±2.2	0.05
<500/μL	4.2±2.7	5.7±3.1	0.027
Days to platelets (mean value ± sd)			
>30×10^9/L	12.9±2.2	13.1±5.1	ns
>50×10^9/L	14.6±2.8	15.9±6.9	ns
>100×10^9/L	17.6±3.8	23.2±19.6	ns

Incidence of mucositis, fever, and toxicity and hospital stay analysis

WHO grades II-IV mucositis was observed in 32 cases, 16 of which in the MIOM group and 16 in the TIM group (*p*=ns, Table 3). Furthermore, no significant difference was observed in the duration of mucositis between the two groups. The incidence of fever was unexpectedly lower in MIOM cases (48.3%) than in TIM cases (75%, *p*=0.02). No difference was observed in mean duration of fever (Table 3). Finally, bacteremia was documented in only one MIOM case whereas it occurred in 7 inpatient cases. Other non-hematologic transplant-related toxicities were very low and similarly distributed between the two groups. In this regard, 1 pulmonary thromboembolic event was documented in the MIOM group (2 in the TIM group). There was one transplant-related death in the MIOM group. Platelets were basically administered at a platelet count below 20×10^9/L. A significantly lower number of platelet units was infused in the outpatient setting and 20% of MIOM patients did not require

Table 3. Comparison of toxicity and supportive care between TIM and MIOM.

Variables	*MIOM*	*TIM*	*p*
Mucositis grade II-IV			
No	44	24	ns
Yes	16	16	
Days on mucositis (mean value ± sd)	2.7±2.5	3.2±3.1	ns
Fever >38°C			
No	31	10	0.02
Yes	29	30	
Days on fever (mean value±sd)	3.8±1.8	3.8±1.7	ns
Packed red cell transfusions, median value (range)	0 (0-8)	1 (0-19)	0.018
Platelet transfusions, median value (range)	1(0-8)	3 (0-32)	<0.0001

Table 4. Univariate and logistic multivariate regression analysis of risk factors for development of fever.

Variable	*Fever*		**Univariate*	*°Multivariate*
	yes	*no*	*p*	*p*
Age, years (< 54 v ≥ 54)	27 v 32	16 v 25	0.5	–
Sex (male v female)	37 v 22	28 v 13	0.6	–
No. of infused $CD34^+$ cells $\times 10^6$/Kg (< 5 v ≥ 5)	22 v 37	15 v 26	1.0	–
Disease status at PBSCT (responders v non responders)	45 v 14	32 v 9	0.4	–
PBSCT (1^{st} v 2^{nd} v 3^{rd})	38 v 17 v 4	17 v 18 v 5	0.1	0.1
MIOM v TIM)	29 v 30	31 v 10	0.02	0.1
Days to ANC>100/μL (< 9 v ≥ 9)	5 v 54	11 v 30	0.017	0.1
Mucositis grade II-IV (no v yes)	30 v 29	37 v 4	<0.0001	0.002

**Fisher's exact test; °Logistic regression analysis.*

platelet transfusions whereas only 3% of the TIM group did not require platelet transfusions (Table 3). Similarly, a significantly lower number of packed red cell transfusions was required by outpatients (Table 3), probably due to a higher number of outpatients treated with erythropoietin (*data not shown*).

Univariate analysis showed that, among variables analyzed, the first PBSCT, TIM, 9 or more days to reach an absolute neutrophil count ≥ 100/μL, and mucositis grades II-IV were associated with a higher risk of fever development (Table 4). However, mucositis remained the sole independent predictor in multivariate analysis (p=0.002).

In the MIOM group, 30 (50%) cases never required re-admission after stem cell infusion and were followed-up in a Day Hospital setting a median of 9 times. Four cases were not discharged (median duration of hospital stay 15 days). The remaining 26 cases were re-admitted with a median overall hospital stay of 9 days. Reasons for hospitalization were mostly continuous fluid replacement or slow response to first line antibiotic therapy. Of note, the median time to discharge of TIM cases was 20 days.

Discussion

In this study, we describe an outpatient program for high-dose melphalan and supportive care after PBSCT in MM patients. This model was mainly sustained by the growing demand for PBSCT in MM and by continuous cost containment pressures. In this regard, Barosi *et al*. reported that the length of hospitalization accounts for the most onerous part of the cost of a stem cell transplantation in an Italian institution.[23] In the United States, the management of myeloma transplants in an outpatient setting has allowed significant financial savings, mainly due to reduced length of hospitalization and lower drug and laboratory costs.[24]

Three different programs for outpatient care have been described in literature. In the early-discharge model, in which only high-dose therapy is planned in an inpatient setting,[25] Peters *et al*. reported a 28.5% reduction of days of hospitalization. Conversely, in the delayed admission model, patients were hospitalized only during the aplastic phase and their median duration of hospital stay was reduced to 2 weeks.[26] Finally, the total outpatient model, the most extensive approach to outpatient care, is associated with the shortest duration of hospitalization.[27-29] Our MIOM basically resembles this last model, in that both high-dose melphalan administration and supportive care management are carried out in the outpatient setting, reserving hospitalization for complicated patients. It is worth noting that stem cells are infused in the inpatient bone marrow transplant unit. Although we made this procedure very safe by depleting DMSO from apheretic products,[22] the choice to infuse stem cells in the inpatient unit was exclusively due to Italian administrative practices. Our results clearly indicate that MIOM cases, homogeneously rescued with a relatively high number of PBSC after high dose melphalan, had a significant reduction of hospitalization and no suggestion of increased toxicity. Of note, only 6.7% of cases were not discharged, and the 43% who were re-admitted had a median hospital stay of 9 days, which is significantly shorter than the median 20

days before TIM cases are discharged home. Furthermore, a significantly higher incidence of fever was unexpectedly documented among inpatient transplant recipients. However, grade II-IV mucositis remained the only variable significantly predicting fever development in multivariate analysis, confirming that the option of MIOM *per se* has no impact on fever development. These data are in line with Jagannath's report, in which no differences were demonstrated in hematopoietic recovery and non-hematologic toxicity. In Jagannath's study, only 21% of the outpatient population required admission after transplantation.[24]

The first conclusion that we can draw is that a positive-pressure reverse isolation room during the neutropenic period is not mandatory. This finding should offset the reconstruction of the global outpatient care model, requiring extensive coordination and implementation of resources. However, outpatient care that functioned 12 hours/day with extra time during the week-end was essential for our MIOM of management. Our organization was in line with that proposed by Peters *et al*.,[25] with minimal home health care support, and different from Geller's model,[29] in which no home assessments were programmed. Besides anxiety or the patient's refusal due to concerns regarding surveillance, the lack of a caregiver and financial limitation are clearly two major obstacles which preclude outpatient care for PBSCT.[30] In our series, no refusal was due to the lack of a caregiver, possibly due to social reasons, while the MIOM was applicable in 49 transplants thanks to the temporary local housing CASAIL project. It is worth noting that outpatients managed in CASAIL had a 42.5% incidence of fever, as compared with the 64.7% in outpatients managed at home and the 75% among inpatients, with no difference in mean duration of fever. This quite unexpected finding clearly shows that CASAIL, with its environment, cleaning facilities and minimization of contact with people, is at least comparable with an inpatient ward.

We did not perform a formal study dealing with quality of life. However, this aspect should be explored, since the feeling is that MIOM patients might have a better perception of well-being than do those transplanted in the TIM context. This sensation is in line with a recent report dealing with a comparison between the psychosocial impact of inpatient-outpatient autologous transplants.[31] In this study, Summers *et al*. found that outpatients had significantly higher scores for emotional well-being and global quality of life than did inpatients.[31]

At this point, two issues should be discussed. First, mucositis prophylaxis seems to be the most important aspect to be seriously re-considered in the context of outpatient transplants. In our study, a previously described magnesium chloride-containing solution[32] was used for mucositis prophylaxis in all patients. However, new attempts should be considered to improve results. In this regard, administration of cytoprotectors, although expensive, might reduce the severity of chemotherapy-related mucositis.[33,34] Second, fever was managed with a single antibiotic as first-line treatment in the majority of cases[35] and very few cases needed combination therapy for fever resolution. There was a lower incidence of microbiologically documented fever in the MIOM group, probably due to the lower intensity of microbiological surveillance. Since fever was dealt with in the same manner in the 2 groups and there was no difference in its duration, the use of a single antimicrobial agent and limited numbers of blood cultures should translate into savings in both costs and time for the outpatient setting.[36]

Another interesting issue is the potential use of erythropoietin to reduce transfusion requirements. In this study, a significantly lower number of packed red cell transfusions were required by outpatients, due to a recent common practice in our center of administering erythropoietin before PBSCT. This finding should be taken into consideration in the global therapeutic approach to PBSCT. Finally, in the light of the promising results obtained by allogeneic bone marrow transplantation with a reduced intensity conditioning regimen for MM,[37] for such patients we are developing a similar outpatient care program.

In conclusion, an outpatient transplant program using HDM is feasible. Our findings, together with reports from literature, support the hypothesis that a total therapeutic program for MM patients may be performed in an outpatient setting. It is reasonable to foresee that high-dose therapy be transferred to hematologic centers with sufficient know-how to guarantee savings while improving the quality of the patients' care. The expensive structures of the bone marrow transplant units may be reserved for higher risk transplantations.

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FM, MM, EO, CS, MR, MK, GI, GC, MF, GM, SM and VC conceived and designed the study, revised the article critically and approved the version to be published. FM, MM, EO and PI analyzed and interpreted the data; FM, Eo and PI drafted the article. FM takes primary responsibility for the paper. All tables were created by FM.

Disclosures

Conflict of interest: none.

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References

1. Hallek M, Bergsagel PL, Anderson KC. Multiple myeloma: increasing evidence for a multistep transformation process. Blood 1998; 91:3-21.
2. Bataille R, Harousseau JL. Multiple Myeloma. N Engl J Med 1997; 336:1657-64.
3. Anonymous. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol 1998; 16:3832-42.
4. Cunningham D, Paz AL, Milan S, Malpas J, Hickish T, Nicolson M, et al. High-dose melphalan and autologous bone marrow transplantation as consolidation in previous untreated myeloma. J Clin Oncol 1994; 12:759-63.
5. Barlogie B, Jagannath S, Desikan KR, Mattox S, Vesole D, Siegel D, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 1999; 93:55-65.
6. Tribalto M, Amadori S, Cudillo L, Caravita T, Del Poeta G, Meloni G, et al. Autologous peripheral blood stem cell transplantation as first line treatment of multiple myeloma: an Italian multicenter study. Haematologica 2000; 85:52-8.
7. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myelome. N Engl J Med 1996; 335:91-7.
8. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Intergroupe Francophone du Myelome. Blood 2002; 99:731-5.
9. Barlogie B, Jagannath S, Vesole DH, Naucke S, Cheson B, Mattox S, et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood 1997; 89:789-93.
10. Attal M, Harousseau JL, Facon T. Single versus double transplant in myeloma: a randomised trial of the IFM. Proceed VIIIth International Myeloma Workshop. 2001; S15:28.
11. Seregen CM, Sonneveld P, van der Holt P, Vellenga E, Croockewit AJ, Verhoef GE, et al. Intensive versus double intensive therapy in previously untreated multiple myeloma: a prospective randomized phase III study in 450 patients. Proceed VIIIth International Myeloma Workshop. 2001; S17:31.
12. Cavo M, Tosi P, Zamagni E, Ronconi S, Cellini C, Cangini D, et al. The Bologna 96 clinical trial of single versus double PBSC transplantation for previously untreated MM: results of an interim analysis. Proceed VIIIth International Myeloma Workshop. 2001; S16:29-30.
13. Fernand JP, Marolleau JP, Alberti C, Divine M, Leblond V, Macro M, et al. Single versus tandem high dose therapy supported with autologous stem cell transplantation using unselected or CD34 enriched ABSC: preliminary results of a two by two designed randomised trial in 23 young patients with multiple myeloma. Proceed VIIIth International Myeloma Workshop. 2001; P6:147.
14. Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA, Ferrant A, et al. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet 1996; 347:353-7.
15. Rizzo JD, Vogelsang GB, Krumm S, Frink B, Mock V, Bass EB. Outpatient-based bone marrow transplantation for hematologic malignancies: cost saving or cost shifting? J Clin Oncol 1999; 17:2811-8.
16. Hartmann O, Le Corroller AG, Blaise D, Michon J, Philip I, Norol F, et al. Peripheral blood stem cell and bone marrow transplantation for solid tumors and lymphomas: hematologic recovery and costs. Ann Intern Med 1997; 126:600-7.
17. Tarella C, Castellino C, Locatelli F, Caracciolo D, Corradini P, Falda M, et al. G-CSF administration following peripheral blood progenitor cell (PBPC) autograft in lymphoid malignancies: evidence for clinical benefits and reduction of treatment costs. Bone Marrow Transplant 1998; 21:401-7.
18. Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 1998; 16:1179-87.
19. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after bone marrow transplantation: a prospective, randomized, double-blind study. J Infect Dis 1995; 171:1545-52.
20. Morabito F, Irrera G, Oliva E, Console G, Martino M, Pucci G, et al. Infectious complications in breast cancer patients undergoing peripheral blood stem cell transplantation: a single center retrospective abalysis towards outpatient strategy. Bone Marrow Transplant 2001; 28:883-8.
21. Dix SP, Geller RB. High-dose chemotherapy with autologous stem cell rescue in the outpatient setting. Oncology 2000; 14:171-85.
22. Martino M, Morabito F, Messina G, Irrera G, Pucci G, Iacopino P. Fractionated infusions of cryopreserved stem cells may prevent DMSO-induced major cardiac complications in graft recipients. Haematologica 1996; 81:59-61.
23. Barosi G, Marchetti M, Alessandrino P, Locatelli F, Casula S, Lunghi M, et al. A model for analysing the cost of autologous peripheral blood progenitor cell (PBPC) transplantation. Bone Marrow Transplant 1999; 23:719-25.
24. Jagannath S, Vesole DH, Zhang M, Desikan KR, Copeland N, Jagannath M, et al. Feasibility and cost-effectiveness of outpatient autotransplants in multiple myeloma. Bone Marrow Transplant 1997; 20:445-50.
25. Peters WP, Ross M, Vrendenburgh JJ, Hussein A, Rubin P, Dukelow K, et al. The use of intensive clinic support to permit outpatient autologous bone marrow transplantation for breast cancer. Semin Oncol 1994; Suppl 7:25-31.
26. Weaver CH, Schwartzberg L, Zhen B, Mangum M, Leff R, Tauer K, et al. High-dose chemotherapy and peripheral blood stem cell infusion in patients with non-Hodgkin's lymphoma: results of outpatient treatment in community cancer centers. Bone Marrow Transplant 1997; 20:753-60.
27. Meisenberg BR, Miller WE, McMillan R, Callaghan M, Sloan C, Brehm T, et al. Outpatient high-dose chemotherapy with autologous stem cell rescue for hematologic and non-hematologic malignancies. J Clin Oncol 1997; 15:11-7.
28. Gluck S, des Rochers C, Cano C, Dorreen M, Germond C, Gill K, et al. High-dose chemotherapy followed by autologous blood cell transplantation: a safe and effective outpatient approach. Bone Marrow Transplant 1997; 20:431-4.
29. Geller RB, Dix SP, Belt RJ, et al. Minimum resource utilization for patients with breast cancer, lymphoma, or multiple myeloma undergoing mobilization and high-dose chemotherapy followed by peripheral blood stem cell transplants as outpatients. Blood 1997; 90:370[abstract].
30. Sharma N, Hendrix L, O'Connell K. Obstacles to performing high-dose therapy with peripheral blood stem cell rescue in

the outpatient setting. Blood 1997; Suppl 1:116[abstract].
31. Summers N, Dawe U, Stewart DA. A comparison of inpatient and outpatient ASCT. Bone Marrow Transplant 2000; 26: 389-95.
32. Rossetti A, Azzarà M, Castiglione S, et al. Low incidence of mucositis using a new compound (magnesium chloride) for mucositis prevention after allogeneic BMT and autologous PBSCT. Bone Marrow Transplant 1997; 19 Suppl 1:[abstract 22].
33. Karthaus M, Rosenthal C, Ganser A. Prophylaxis and treatment of chemo- and radiotherapy-induced oral mucositis – are there new strategies? Bone Marrow Transplant 1999; 24:1095-108.
34. Capelli D, Santini G, De Souza C, Poloni A, Marino G, Montanari M, et al. Amifostine can reduce mucosal damage after high-dose melphalan conditioning for peripheral blood progenitor cell autotransplant: a retrospective study. Br J Haematol 2000; 110:300-7.
35. Kurthaus M, Wolf HH, Kampfe D, Egerer G, Ritter J, Peters G, et al. Ceftriaxone monotherapy in the treatment of low-risk febrile neutropenia. Chemotherapy 1998; 44:343-54.
36. Serody JS, Berrey MM, Albritton K, O'Brien SM, Capel EP, Bigelow SH, et al. Utility of obtaining blood cultures in febrile neutropenic patients undergoing bone marrow transplantation. Bone Marrow Transplant 2000; 26:533-8.
37. Badros A, Barlogie B, Siegel E, Cottler-Fox M, Zangari M, Fassas A, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after non-myeloablative conditioning. J Clin Oncol 2002; 20:1295-303.

Peer Review Outcomes

Manuscript processing

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What is already known on this topic

Thanks to the use of peripheral blood stem cells, time to hematopoietic reconstitution after autologous transplantation has been significantly reduced. Therefore, several investigators have tested the feasibility of performing autologous transplantation on an outpatient basis (partial or total).

What this study adds

In this paper Morabito *et al.* have used a mixed inpatient-outpatient model for 60 autologous transplantations in 29 patients with multiple myeloma. Half of the cases never required readmission and, compared to in a traditional inpatient model, fever episodes were less frequent.

Potential implications for clinical practice

This program can safely be offered to patients with multiple myeloma. This could produce a better quality of life and a reduction of costs.

Jean Luc Harousseau, Associate Editor
(Nantes, France)