Very Low Rate of Readmission after an Early Discharge Outpatient Model for Autografting in Multiple Myeloma Patients: An Italian Multicenter Retrospective Study

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Abstract

We analyzed the main modalities and clinical outcomes of the early discharge outpatient model in autologous stem cell transplantation (EDOM-ASCT) for multiple myeloma in Italy. EDOM-ASCT was employed in 382 patients, for a total of 522 procedures, between 1998 and 2012. Our study showed high homogeneity among centers in terms of inclusion criteria, supportive care, and in hospital readmission criteria. Overall, readmissions during the aplastic phase occurred in 98 of 522 transplantations (18.8%). The major extrahematological complication was neutropenic fever in 161 cases (30.8%), which required readmission in 76 cases. The incidence of severe World Health Organization grade 3 to 4 mucositis was 9.6%. By univariate analysis, fever, mucositis, altered renal function at diagnosis, second transplantation, and transplantation performed late in the course of the disease were significantly correlated with readmission, whereas fever, mucositis, altered renal function, and timing of transplantation remained the only independent predictors by multivariate analysis. Overall, transplantation-related mortality was 1.0%. No center effect was observed in this study (P = .36). The safety and low rate of readmission of the EDOM-ASCT in myeloma trial suggest that this strategy could be extended to other transplantation centers if a stringent patient selection and appropriate management are applied.

ntroduction

High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) 1 and 2 remains the standard of care for young medically fit patients with multiple myeloma (MM) 3, 4 and 5. Recent studies also suggest that induction therapy with so-called new drugs before transplantation may improve clinical outcomes 6 and 7. In addition, long-term disease control can be achieved with a variety of post-transplantation consolidation [8] and maintenance therapies 9 and 10. Up until now, it is, however, not clear how proteasome inhibitor and immunomodulatory drugs should be best incorporated in the transplantation paradigm [11]. Moreover, whether ASCT should be maintained as an upfront strategy or delayed until relapse is a matter of debate 12 and 13. Overall, the International Myeloma Working Group recommends that ASCT be invariably offered at some point during the disease course for eligible young patients [14]. Thus, MM remains the leading indication for ASCT in Europe [15].

Patients undergoing ASCT are usually admitted to bone marrow transplantation units on a “whole inpatient program,” where central venous catheter (CVC) insertion, HDC administration, hematopoietic progenitor cell (HPC) infusion, and supportive care during neutropenia are carried out in positive-pressure reverse isolation rooms, with a hospital stay of approximately 3 to 4 weeks 15, 16 and 17. The growing demand for ASCT significantly increases waiting lists and generates concerns about the appropriate use of health care resources. Over the past years, a number of studies

have investigated safety, efficacy, and potential cost advantages of outpatient programs to reduce hospital stays after ASCT in both hematological and nonhematological diseases [17]. The early-discharge outpatient model (EDOM) is 1 of the most common approaches. By this model, CVC insertion, fluid infusion, HDC administration, and HPC infusion are carried out as inpatient care, whereas the management of the aplastic phase is carried out as outpatient care. Though many reports suggest its feasibility also in lymphoma patients after BEAM (BCNU, etoposide, cytarabine and melphalan conditioning) 18 and 19, stringent inclusion criteria have not yet been clearly defined, and policies may greatly vary especially for the management of the aplastic phase in the outpatient setting and for readmission criteria. The aim of this study was to retrospectively evaluate current policies and to analyze clinical outcomes of EDOM-ASCT in a large cohort of MM patients treated in Italian centers affiliated with the Gruppo Italiano per il Trapianto di Midollo Osseo (GITMO).

Material and Methods

This retrospective study was conducted through the GITMO trial office, which promotes independent clinical research studies in the setting of both autologous and allogeneic transplantation in Italy. The first questionnaire was mailed to 75 GITMO centers accredited for ASCT to evaluate how many had been involved in EDOM-ASCT for MM patients between 1998 and 2012. In all centers, eligibility to the EDOM program included availability of a caregiver on a 24-hour basis; housing within easy reach to the transplantation center (shorter than 1 hour drive); absence of multiple comorbidities as assessed by the treating physician; a baseline serum creatinine value < 2 mg/dL at transplantation; adequate activities of daily living, such as eating, cleaning, personal hygiene, and ambulation possible independently or under the supervision of a caregiver; and informed consent for the EDOM-ASCT program. If a given center was involved, further specific queries included infectious prophylaxis, supportive care, criteria for hospital readmission, management of febrile neutropenia, and clinical outcomes.

Overall, 55 of 75 (73.3%) answered the first questionnaire: 49 centers performed ASCT after the inpatient procedure and 6 had been involved in outpatient ASCT programs according to EDOM.

Endpoints

Primary endpoints were to evaluate efficacy and safety of EDOM-ASCT in terms of rates of hospital readmission before neutrophil and platelet recoveries and early transplantation-related mortality (TRM). Neutrophil and platelet recoveries were defined as the first of 3 consecutive days of an absolute neutrophil count $\geq .5 \times 10^9$/L and the first of 3 days of a platelet count $\geq 20 \times 10^9$/L without transfusion support for 7 consecutive days. Early TRM was defined as mortality from any cause other than disease progression within 100 days from transplantation. Secondary endpoints were to investigate differences in center policies for patient inclusion criteria in EDOM-ASCT, supportive care, hospital readmission criteria, and to collect clinical data on incidence of infections, days of fever, hematological, and extrahematological toxicities, progression-free survival (PFS), and overall survival (OS). The ultimate goal was that of collecting robust information on the feasibility of EDOM-ASCT to help design clinical recommendations in our country. The study was approved by the local ethics committee of the 6 participating centers and conducted according to the Declaration of Helsinki.

Statistical Analysis

Data are summarized as median and interquartile ranges or as absolute number or percent frequency, as appropriate. The relationship between risk factors and the odds of hospital

readmission before neutrophil and platelet recoveries were investigated by univariate and multivariate logistic regression analyses. Tested variables included gender, age, fever, World Health Organization (WHO) grade 3 to 4 mucositis, renal function (serum creatinine level < 2 mg/dL versus ≥ 2 mg/dL), number of $CD34^+$ cells infused, granulocyte-colony stimulating factor (G-CSF) (filgrastim and lenograstim) versus pegfilgrastrim, first versus second transplantation, timing of transplantation, conditioning regimen, and disease status at transplantation. All variables correlated with hospital readmission with a *P* value of ≤ .10 were analyzed by a multiple logistic regression model. With this strategy, the model had adequate statistical power with at least 20 readmitted patients for each variable added to the final model. All *P* values were 2-sided at the 10% significance level, as suggested by McDonald et al. [20]. In both univariate and multivariate logistic regression models, data were expressed as odds ratio (95% confidence interval [CI] and *P* values). To ascertain the effect of repeated observations in the same patients who may have undergone more than 1 transplantation, a sensitivity analysis was performed by restricting the focus only on the first transplantation. A center-effect analysis was also carried out by comparing the point estimates and the 95% CI of the percentages of patients who were readmitted at the participant centers. One center (Potenza) was excluded by this analysis because of the low number of patients enrolled (n = 4). OS and progression-free survival curves were estimated by the Kaplan-Meier method. Data analysis was performed by SPSS for windows (version 20.0.0, IBM, Armonk, NY).

Results

Overall, between January 1998 and December 2012, 536 EDOM-ASCT procedures for 382 MM patients were performed at Italian GITMO centers. Fourteen cases (2.6%) with incomplete data set for the evaluation of primary endpoints of the study were excluded from the analysis, leaving 522 eligible, representing the body of this paper. Center activities are illustrated in Figure 1 and patient characteristics are summarized in Table 1.

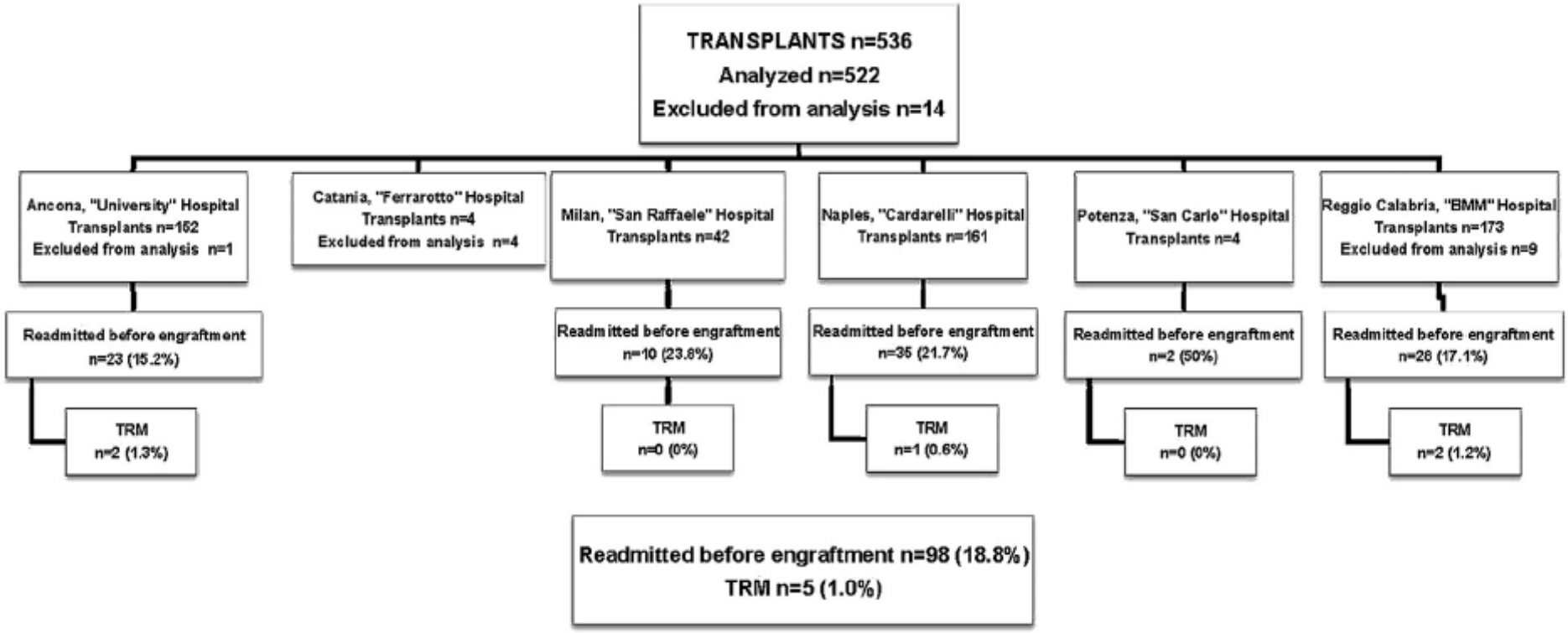

Figure 1. Retrospective Italian multicenter analysis of patients with multiple myeloma who underwent an autologous hemopoietic progenitor cell transplantation after an early discharge outpatient model between January 1998 and December 2012.

Table 1
Characteristics of Multiple Myeloma Patients Undergoing an EDOM-ASCT

Characteristic	Value
Total no. of patients	382
Sex, n (%)	
Male	253 (66.2)
Female	129 (33.8)
Age, median (range), yr*	58.7 (27.5-75.4)
Gammopathies, n (%)†	
IgG	209 (54.7)
IgA	79 (20.7)
Light chain	74 (19.4)
Not known	20 (5.2)
Gammopathies, n (%)‡	
κlight chain	207 (54.2)
λlight chain	145 (38.0)
Not known	30 (7.9)
Renal function (Durie and Salmon subclassification criteria), n (%)	
Serum creatinine level < 2 mg/dL	270 (70.7)
Serum creatinine level ≥ 2 mg/dL	65 (17.0)
Not known	47 (12.3)
Induction regimen schedule, n (%)	
VAD (vincristine, doxorubicin and dexamethasone)	202 (52.9)
Velcade-based	114 (29.8)
Imids-based	55 (14.4)
Others	11 (3.2)
Up-front transplantation§, n (%)	304 (79.6)
Status after induction regimen, n (%)‖	
Complete response	92 (24)
Near complete response	23 (6)
Very good partial response	73 (19)
Partial response	175 (46)
Stable disease	11 (3)
Progression disease	8 (2)
Outpatient procedures	
At the first ASCT	350 (67.0)
At the first and second ASCT	140 (26.8)
At the second ASCT	32 (6.2)
Total number of ASCT	522 (100)
Conditioning regimen, n (%)	
Melphalan 200 mg/m^2	437 (84)
Melphalan 140 mg/m^2	85 (16)

EDOM indicates early discharge outpatient model; ASCT, autologous stem cell transplantation.

* Data are shown as median (interquartile range).
† Measured by serum immunofixation or immunoelectrophoresis.
‡ Measured by urine immunofixation or immunoelectrophoresis.
§ Transplantation at diagnosis.
‖ Clinical response evaluated using the European Group for Blood and Marrow Transplantation Criteria.

Median age at transplantation was 58.7 (range, 27.5 to 75.4) years, and the majority of patients were male (66.2%). At diagnosis, serum creatinine level was < 2 mg/dL in 270 of 382 (70.7%) patients, and ≥ 2 mg/dL in 65 of 382 (17%) [21]. Data were missing in 47 of 382 (12.3%). Most patients (52.9%) received vincristine, adriamycin, and dexametasone–based induction regimens. Response rates by the European Society for Blood and Marrow Transplantation criteria [22] are described in Table 1. High-dose melphalan (HDM) 200 mg/m^2 (84%) or 140 mg/m^2 (16%) were employed as conditioning. All patients received HPC with a median dose of CD34$^+$ cells of 5.0 (range, 1.2 to 15.0) × 10^6/kg. Discharge after the HPC infusion occurred at a median of 1 day (range, 0 to 3).

Supportive Care

During the aplastic phase, all patients received oral prophylaxis with ciprofloxacin at 500 mg twice daily or levofloxacin at 500 mg/day from day 0 until neutrophil recovery, and with acyclovir at 800 mg twice daily from day +3 post-transplantation until approximately day +90. *Pneumocystis Jiroveci* prophylaxis with trimethoprim/sulfamethoxazole, 1 double-strength tablet 2 or 3 times weekly, was started after hematological recovery and continued for 3 months. Antifungal prophylaxis with fluconazole at 400 mg/day was started at day 0 and continued until neutrophil recovery only in 2 centers (Milan, San Raffaele Hospital, and Naples, Cardarelli Hospital). All centers except 1 used cryotherapy with ice chips for the prevention of HDM-induced oral mucositits. Patients started keeping ice chips in their mouths approximately 30 minutes before the HDM conditioning and for about 6 hours afterwards. At the University Hospital center in Ancona, amifostine at 750 mg/m^2 was administered before HDM conditioning to prevent mucositis. G-CSF (filgrastim or lenograstim) at 5 mcg/kg/day was started at day +5 until neutrophil recovery in 217 of 522 transplantations (42%) and single-dose pegfilgrastim at day +1 in 305 of 522 transplantations (58%). Red blood cell and platelet transfusions were given to maintain hemoglobin levels > 8 mg/dL and platelet counts >10 × 10^9/L, or in case of symptomatic anemia and/or minimal muco-cutaneous hemorrhagic syndrome. Patients received i.v. hydration and electrolyte support as per institutional policy.

Criteria for Hospital Readmission

In all centers, criteria for readmission after early discharge included uncontrolled nausea and/or vomiting, diarrhea and/or severe mucositis requiring continuous fluid replacement, continuous need of parental nutrition or narcotic drugs, pneumonia, cardiac and/or respiratory distress, patient request, or any other toxicity judged unmanageable as outpatient by the medical staff. Fever without hemo-dynamic instability responsive to first-line antibiotics was managed on the outpatient service, except at the San Raffaele Hospital in Milan where patients were hospitalized.

Management of Febrile Neutropenia

In all centers, neutropenic fever (NF) was defined as an axillary temperature exceeding > 38.2°C on at least 2 consecutive occasions or a persistent temperature of equal to or greater than 38.0 C° for at least an hour, in the absence of any documented noninfectious cause, such as transfusion reactions or administration of cytotoxic drugs. Neutropenia, again, was defined as absolute neutrophil count < .5 × 10^9/L or absolute neutrophil count of 1 and a predicted decline to less than .5 over the next 48 hours. When NF was observed, blood and catheter cultures were set up and empiric antibiotic therapy was promptly started. Patients received i.v. ceftriaxone at Cardarelli Hospital in Naples, at BMM Hospital in Reggio Calabria, and at San Carlo Hospital in Potenza, i.v. piperacillin-tazobactamat San Raffaele Hospital in Milan, or oral amoxicillin and clavulanic acid at University Hospital in Ancona.

Transplantation Details

Median day of discharge was day 1 (range, 0 to 3) after HPC reinfusion. Neutrophil and platelet engraftment occurred in all patients at a median of 10 (range, 8 to 24) and 12 days (range, 8 to 36 days) after ASCT, respectively. Median numbers of transfused red blood cell and platelet units were 0 (range, 0 to 11 units) and 0 (range, 0 to 7 units), respectively (Table 2). Transfusion support was not statistically different in the setting of patients who required a rehospitalization (data not shown). Readmission until neutrophil and platelet recovery was required in 98 out of 522 transplantations (18.8%) (Figure 1). Readmission rates did not significantly differ among the centers and a center effect was not observed (Figure 2). The major extrahematological complication was NF in 161 cases (30.8%) and was the main reason for readmission in 76 cases, whereas the remaining 85 cases were managed as outpatients. Median number of days of fever and antibiotic therapy was 3 (range, 1 to 22) and 6 (range, 0 to 25), respectively. In most cases (82%), no documented infections were reported. Infections documented by blood and/or urine or sputum cultures, or suggested by imaging studies, such as chest radiographs, and physical examination (ie, cellulites around the catheter exit sites) in the absence of positive cultures, were reported in 4% and 8% of febrile episodes, respectively. In 6.2% of cases, cultures from indwelling intravenous catheters yielded coagulase-negative *Staphylococci* CVC-related infections. In the remaining 361 procedures (69.2%), no fever was reported during neutropenia. No systemic fungal infections, either possible or probable, could be documented. Severe WHO 3 to 4 mucositis, according to the WHO's grading scale [23], was reported in 50 cases (9.6%). Other extrahematological toxicities were infrequent and rarely caused readmission (Table 3). Five patients (1%) died within 100 days from transplantation. One patient, readmitted 4 days after discharge for NF, died on day 25 after ASCT for hemorrhagic stroke. Three patients died of sepsis: 1, readmitted at day 5, died of sepsis and respiratory failure on day 30; 1 died on day 7 with documented infection by *Escheria coli*, and in another, who died on day 15, no pathogen was identified. One additional patient developed a clinically documented infection (pneumonia) and died on day 12 after ASCT. In all cases, autopsy was not performed.

Table 2
Outcome of EDOM-ASCT in Multiple Myeloma Patients in Italy

	Value
No. of transplantations	522
$CD34^+$ cells ($\times 10^6$/kg) infused*	5 (1.2-15)
Duration of hospitalization (day)*	4 (2-9)
Day of discharge*,†	1 (0-3)
Type of G-CSF, n (%)	
Filgrastim/lenograstim	217 (42)
Pegfilgrastim	305 (58)
Erythrocyte transfusions (units), n*	0 (0-11)
Platelet transfusions (units), n*	0 (0-7)
Engraftment (days after transplantation)*	
Days to reach neutrophils $>.5 \times 10^9$/L	10 (8-24)
Days to reach platelets $> 20 \times 10^9$/L	12 (8-36)

EDOM indicates early-discharge outpatient model; ASCT, autologous stem cell transplantation.

* Data are shown as median (interquartile range).

† Day of discharge after transplantation, ie, day 0 is the day of stem-cell reinfusion.

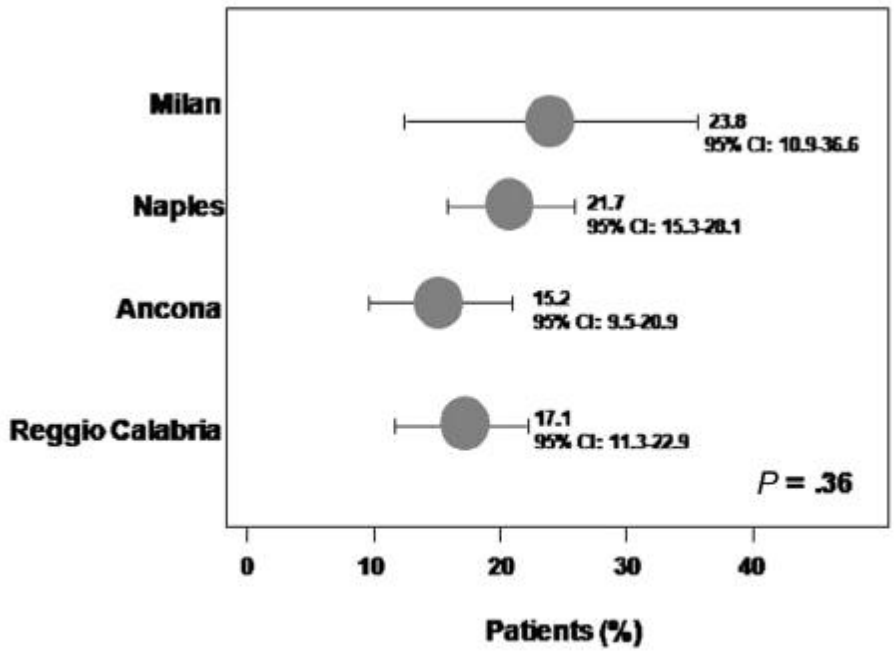

Figure 2. Readmission before engraftment (neutrophils $> .5 \times 10^9$/L and platelets $> 20 \times 10^9$/L).

Table 3
Toxicity of EDOM-ASCT in Multiple Myeloma Patients in Italy

	Value
No. of transplantations	522
Fever $\geq$ 38.2°C, n (%)	161 (30.8)
Fever origin, n (%)	
FUO	132 (82.0)
CVC related	10 (6.2)
Clinically documented	13 (8.0)
Microbiologically documented infection	6 (4.0)
No. of days of fever $\geq$ 38.2°C*	3 (1-22)
No. of days antibiotic therapy*	6 (0-25)
Mucositis grade 3-4, n (%)	50 (9.6)
Readmitted before ANC $>$ .5, n (%)	98 (18.8)
Reasons for readmission to hospital, n (%)	
Febrile neutropenia	76 (14.6)
Mucositis	9 (1.7)
Diarrhea	9 (1.7)
Arrhythmia	2 (.4)
Transit ischemic attack	1 (.2)
Cutaneous hemorrhage	1 (.2)
Duration of second hospitalization, d*	8 (1-30)

EDOM indicates early discharge outpatient model; ASCT, autologous stem cell transplantation; ANC, absolute neutrophil count; CVC, central venous catheter; FUO, fever of unknown origin.

* Data are shown as median (interquartile range).

Risk Factors for Readmission

By univariate analysis, gender, age at transplantation, number of $CD34^+$ infused, type of myeloid growth factor, conditioning regimen, and disease status at transplantation had no impact on readmission rate, whereas fever, mucositis, renal function (creatinine level $\geq$ 2 mg/dL at diagnosis), number of ASCT procedures (second), and timing of transplantation (ie, late in the course of the disease, not upfront) were significantly associated with readmission (Table 4). However, by multivariate analysis, only fever, mucositis, altered renal function, and timing of transplantation remained independent predictors. These findings were also confirmed by a sensitivity analysis carried out on patient characteristics at the first transplantation (see Table 4).

Table 4
Univariate and Logistic Multivariate Regression Analysis of Risk Factors for Readmission before Neutrophil and Platelet Engraftment

Risk Factor	Odds Ratio (95% CI) and *P* Value for Readmission	
	Univariate Analysis	Multivariate Analysis*
Female gender	1.39 (.88-2.19), $P = .16$	–
Age, yr	1.02 (.99-1.05), $P = .21$	–
Fever (yes versus no)	12.9 (7.7-21.8), $P < .001$	10.3 (5.2-20.4), $P < .001$
Mucositis WHO 3-4 (yes versus no)	6.5 (3.5-12.4), $P < .001$	5.7 (2.6-12.3), $P < .001$
Renal function (sCr $\geq$ 2 mg/dL versus <2 mg/dL) at diagnosis	1.62 (.92-2.85), $P = .09$	2.21 (.99-4.90), $P = .05$
$CD34^+$ cells ($\times 10^6$/kg) infused ($\geq$5 versus < 5)	.90 (.58-1.40), $P = .64$	–
G-CSF versus pegfilgrastim	.72 (.46-1.12), $P = .15$	–
Number of transplantations (second versus first)	.67 (.41-1.09), $P = .10$	.64 (.31-1.30), $P = .22$
Timing of transplantation (up-front versus delayed)	.61 (.37-1.00), $P = .05$	.35 (.15-.81), $P = .01$
Conditioning regimen (Mel 140 versus 200)	1.29 (.74-2.25), $P = .37$	––
Status at transplantation		
Complete remission†	1	––
Near complete remission	.54 (.13-2.22), $P = .40$	
Very good partial remission	1.14 (.25-5.33), $P = .87$	
Partial remission	.34 (.08-1.48), $P = .15$	
Stable disease	.69 (.18-2.69), $P = .59$	
Progression	1.08 (.18-6.21), $P = .94$	

sCr indicates serum creatinine; WHO, World Health Organization; G-CSF, granulocyte-colony stimulating factor (filgrastim or lenograstim), Mel, melphalan; CI, confidence interval.
A sensitivity analysis considering patients characteristics at the first transplantation confirmed fever (odds ratio [OR], 12.6; 95% CI, 6 to 26; $P < .001$), mucositis WHO 3 to 4 (OR, 9.5; 95% CI, 3.8 to 23.7; $P < .001$), renal function (OR, 2.4; 95% CI, 1.01 to 5.2; $P = .03$), and timing of transplantation (OR, .40; 95% CI, .17 to .97; $P < .043$) as independent correlates of readmission.
* We included into the multivariate model all variables with $P < .10$ at univariate analyses.
† Reference group.

Clinical Outcomes

At a median follow-up of 200 months, OS and PFS were 85 months (95% CI, 76 to 93) and 34 months (95% CI, 29 to 38), respectively. At follow-up, 20% of the patients were alive and 18% had not progressed (Figure 3).

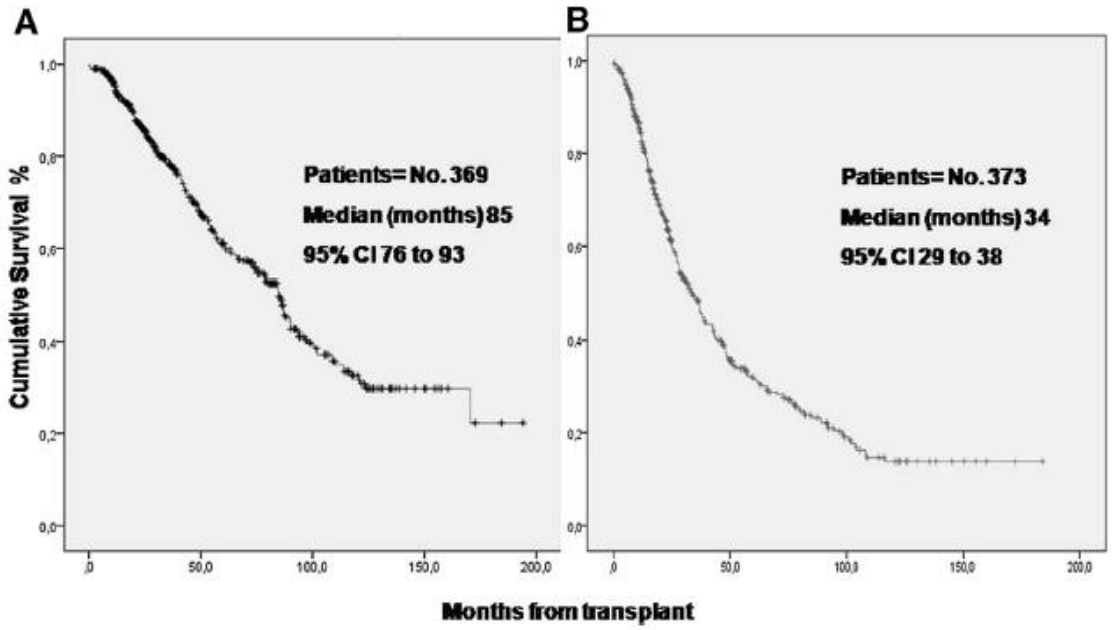

Figure 3. Kaplan-Meier estimates of overall survival (A) and progression-free survival (B) in the evaluable population.

Discussion

The aim of this study was to evaluate the current role of EDOM-ASCT and to analyze clinical outcomes on a large patient cohort in centers with long-standing experience in MM treatment. Despite the retrospective nature of the study, it was rather remarkable to observe that the centers involved shared similar patient selection criteria, antimicrobial prophylaxis, and hospital readmission strategies.

The weakness of the study is the lack of a control group. A formal randomization could not be carried out, given that the primary endpoint was the feasibility of the EDOM-ASCT program and a retrospective data collection for a case-match analysis would not be possible in all centers. However, the data reported here, in terms of outcome, engraftment kinetics, TRM, and toxicity, are comparable with the main series recently reported in the literature 11, 14 and 24. Several manuscripts have already demonstrated that the outpatient program is feasible [17] and, in some studies, a clinical advantage has been shown as well as the saving of financial resources 25, 26 and 27. Our paper, through the analysis of a remarkable number of transplantation procedures performed in the Italian centers, is focused on the optimization of the EDOM-ASCT. Therefore, we believe the only meaningful comparison (besides the description of our results) should be performed with similar studies published in the literature. Specifically, in our study, we showed that a high degree of standardized EDOM-ASCT procedures among GITMO centers is feasible, with no significant differences in readmission and TRM rates. Center effects may often represent an important bias in retrospective multicenter studies. Epidemiologists formally assess a potential center effect by comparing point estimates of given variables and corresponding 95% CI. A center effect can reasonably be excluded when CI largely overlap [28]. Large overlapping areas of CI were seen in our analysis, indicating that clinical outcomes were not center dependent (Figure 2).

Overall, unlike other reports 16, 18, 29, 30, 31, 32, 33 and 34, our readmission rate, 18.8%, was quite low. This may be explained by a number of reasons.

First, antimicrobial prophylaxis was routinely administered. A recent meta-analysis [35] of 109 randomized trials in patients who developed neutropenia without fever showed that those with hematological malignancies and/or undergoing HPC transplantation were at higher risk of readmission. Moreover, a lower all-cause mortality was seen in patients on antimicrobial prophylaxis as compared with those who were not. Fernandez Aviles [36] reported a very low readmission rate, 8%, by introducing ceftriaxone prophylaxis in 50 patients with different hematological malignancies, although, in this study, the early discharged patients were selected in the light of their Eastern Cooperative Oncology Group performance status (<2). Finally, other reports have shown a significant reduction in mortality by adding prophylaxis with quinolones [37].

Second, the outpatient management of NF in most cases with oral antibiotics or once-daily i.v. antibiotics largely contributed to the low readmission rate, that, in turn, highly limited the risk of exposure to multidrug-resistant organisms commonly found on hospital wards [38]. In our experience, only patients with NF and/or documented infections associated with hemodynamic instability were hospitalized. A recently published retrospective analysis on EDOM-ASCT in 91 MM patients by a Canadian group [18] concluded that the procedure is safe and cost effective when performed in a weekday clinic, though it is associated with a high readmission rate, 84%, especially in patients over 60 and with disease stage IIB or higher. The high rate may be explained by the inclusion of patients with advanced disease and different NF management. A policy similar to Canadian group for NF management was reported in a retrospective study by Kassar et al. [33], where 58% of the patients receiving ASCT required hospitalization.

Third, our very low rate of WHO grade 3 to 4 oral mucositis, frequently associated with NF and/or infections 31 and 39 may likely be due to cryotherapy (administered in 371 patients) or to the use of amifostine (151 patients). A recent Cochrane review showed that cryotherapy (ice chips) and the administration of keratinocyte growth factor were of some benefit in preventing mucositis [40]. In our study, though not statistically significant, a lower incidence of severe mucositis was observed at the University Hospital of Ancona, where amifostine was routinely used a cyto-protector. However, it did not significantly affect the probability of readmission. Amifostine detoxifies reactive metabolites of platinum and alkylating agents [41] and its potential role in preventing extrahematological toxicity after HDM has been investigated in many studies, with contrasting results [42].

Although our experience includes patients who underwent transplantation over 10 years ago, no major changes in supportive care were introduced over the study period. One change was the introduction of long-active growth factors. Pegfilgrastim was often chosen to favor patient compliance, given its single dose at 6 mg s.c. rather than daily doses of either filgrastim or lenograstim. A systematic review comparing G-CSF and pegfilgrastim in the autologous setting, including a randomized trial of 80 patients, concluded that the 2 growth factors are at least equally effective [43].

Overall, the first experiences of “outpatient autografts” were reported in North America with readmission rates of 30% [29] and 61% [30]. Faucher et al. [16] reported a rate of 86% in the first randomized study comparing EDOM with standard inpatient ASCT in a cohort of 131 patients with nonleukemic malignant diseases. Of note, 33% of patients could not be discharged early because of social or psychological reasons, such as lack of a caregiver or living far away from the transplantation center. In another study by Gertz et al. [34], only 39% of 716 patients completed the procedure without readmission. Patient age (>65 years) and serum creatinine level (≥1.5 mg/dL)

were associated with higher risk of readmission. We think that the stringent application of inclusion criteria, such as normal serum creatinine at the time of transplantation, the availability of a full-time caregiver, and living within 1-hour drive to the transplantation center, formed the basis for the low readmission rate reported by our centers.

Our study was not designed to carry out a detailed cost analysis. However, several studies showed that outpatient models of autografting are highly cost effective, mainly because of shorter duration of hospitalization and reduced drug administration and laboratory costs 25, 26, 27 and 30. One prospective randomized study comparing an outpatient model with conventional inpatient ASCT [16] in patients with malignancies reported an estimated cost saving of 19%. A recent Italian study [19] focused on EDOM in lymphoma patients, conditioned with BEAM (BCNU, etoposide, cytarabine and melphalan) and given amifostine to reduce extrahematological toxicity, reported a very low incidence of severe mucositis and the outpatient treatment plan was successfully completed in two thirds of the patients. Overall, only 26% required a short readmission and this translated into significant cost saving.

In conclusion, this paper showed a high degree of standardized EDOM procedures among the GITMO centers. The safety and low readmission rates may likely have been due to stringent selection criteria. Ideal candidates appeared to be those with good performance status, a full-time caregiver, and those who lived near the transplantation center. Moreover, NF could safely be managed in the outpatient service and the administration of cyto-protectors may have reduced the severity of mucositis and its symptoms. The detailed analysis of these clinical parameters represents the novelty of the paper and makes, in our opinion, this work potentially valuable for clinical transplantation providers. However, our results do not allow us to extensively recommend the EDOM-ASCT program, outside a national policy, and in centers which do not fulfill the criteria of an adequate skilled team and adequate logistics for the managing these patients. Future trials should focus on large prospective multicenter outpatient programs, which may identify patient subgroups who most benefit from this innovative and cost-effective approach.

References

1. M. Attal, J.-L. Harousseau, A.-M. Stoppa, *et al.*

A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma

N Engl J Med, 335 (1996), pp. 91–97

2. J.A. Child, G.J. Morgan, F.E. Davies, *et al.*

High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma

N Engl J Med, 348 (2003), pp. 1875–1883

3. A. Palumbo, S. Bringhen, H. Ludwig, *et al.*

Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN)

Blood, 118 (2011), pp. 4519–4529

4. L. Fratino, M. Rupolo, M. Mazzuccato, *et al.*

Autologous stem cell transplantation as a care option in elderly patients. A review

Anticancer Agents Med Chem, 13 (2013), pp. 1419–1429

5. S. Yaqub, G. Ballester, O. Ballester

Frontline therapy for multiple myeloma: a concise review of the evidence based on randomized clinical trials

Cancer Invest, 31 (2013), pp. 529–537 doi: 10.3109/07357907.2013.840382

6. P. Sonneveld, H. Goldschmidt, L. Rosiñol, *et al.*

Bortezomib-based versus non bortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials

J Clin Oncol, 31 (2013), pp. 3279–3287

7. B. Lupo, A. Palumbo

Lenalidomide in the treatment of young patients with multiple myeloma: from induction to consolidation/maintenance therapy

Adv Hematol, 2012 (2012), p. 906247

8. U.H. Mellqvist, P. Gimsing, O. Hjertner, *et al.*

Nordic Myeloma Study Group. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial

Blood, 121 (2013), pp. 4647–4654

9. M. Attal, V. Lauwers-Cances, G. Marit, *et al.*

IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma

N Engl J Med, 366 (2012), pp. 1782–1791

10. P.L. McCarthy, K. Owzar, C.C. Hofmeister, *et al.*

Lenalidomide after stem-cell transplantation for multiple myeloma

N Engl J Med, 366 (2012), pp. 1770–1781

11. P. Moreau, H. Avet-Loiseau, J.L. Harousseau, M. Attal

Current trends in autologous stem-cell transplantation for myeloma in the era of novel therapies

J Clin Oncol, 29 (2011), pp. 1898–1906

12. L.J. Costa, M.J. Zhang, X. Zhong, *et al.*

Trends in utilization and outcomes of autologous transplantation as early therapy for multiple myeloma

Biol Blood Marrow Transplant, 19 (2013), pp. 1615–1624

13. N.C. Dunavin, L. Wei, P. Elder, *et al.*

Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma

Leuk Lymphoma, 54 (2013), pp. 1658–1664

14. M. Cavo, S.V. Rajkumar, A. Palumbo, *et al.*

International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation

Blood, 117 (2011), pp. 6063–6073

15. A. Gratwohl, H. Baldomero, J. Passweg

Hematopoietic stem cell transplantation activity in Europe

Curr Opin Hematol, 20 (2013), pp. 485–493

16

C. Faucher, A.G. Le Corroller Soriano, *et al.*

Randomized study of early hospital discharge following autologous blood SCT: medical outcomes and hospital costs

Bone Marrow Transplant, 47 (2012), pp. 549–555

17. M. Martino, M. Montanari, B. Bruno, *et al.*

Autologous hematopoietic progenitor cell transplantation for multiple myeloma through an outpatient program

Expert Opin Biol Ther, 12 (2012), pp. 1449–1462

18. A. Holbro, I. Ahmad, S. Cohen, *et al.*

Safety and cost-effectiveness of outpatient autologous stem cell transplantation in patients with multiple myeloma

Biol Blood Marrow Transplant, 19 (2013), pp. 547–551

19 I. Scortechini, M. Montanari, G. Mancini, *et al.*

Conditioning regimen with BCNU, etoposide, cytarabine and melphalan plus amifostine for outpatient autologous stem cell transplant: feasibility and outcome in 97 patients with lymphoma

Leuk Lymphoma (2013 Nov 1) doi: 10.3109/10428194.2013.842989 [E-pub ahead of print]

20. J.H. McDonald

Handbook of biological statistics

(2nd ed.)Sparky House Publishing, Baltimore, Maryland (2009), pp. 15–20

21. B.G. Durie, S.E. Salmon

A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival

Cancer, 36 (1975), pp. 842–854

22. J. Bladé, D. Samson, D. Reece, *et al.*

Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant

Br J Haematol, 102 (1998), pp. 1115–1123

23. E.B. Rubenstein, D.E. Peterson, M. Schubert, *et al.*

Clinical practice guidelines for the prevention and treatment of cancer therapy induced oral and gastrointestinal mucositis

Cancer, 100 (2004), pp. 2026–2046

24. M. Cavo, P. Tosi, E. Zamagni, *et al.*

Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study

J Clin Oncol, 25 (2007), pp. 2434–2441

25. G. Barosi, M. Marchetti, P. Alessandrino, *et al.*

A model for analysing the cost of autologous peripheral blood progenitor cell (PBPC) transplantation

Bone Marrow Transplant, 23 (1999), pp. 719–725

26. V. Mishra, S. Vaaler, L. Brinch

Cost analysis of autologous peripheral blood stem cell transplantation for multiple myeloma

Clin Lab Haematol, 25 (2003), pp. 179–184

27. B.R. Meisenberg, K. Ferran, K. Hollenbach, *et al.*

Reduced charges and costs associated with outpatient autologous stem cell transplantation

Bone Marrow Transplant, 21 (1998), pp. 927–932

28. J. Cuzick

Forest plots and the interpretation of subgroups

Lancet, 365 (2005), p. 1308

29. W.P. Peters, M. Ross, J.J. Vredenburgh, *et al.*

The use of intensive clinic support to permit outpatient autologous bone marrow transplantation for breast cancer

Semin Oncol, 21 (4 Suppl 7) (1994), pp. 25–31

30. S. Jagannath, D.H. Vesole, M. Zhang, *et al.*

Feasibility and cost effectiveness of outpatient autotransplants in multiple myeloma

Bone Marrow Transplant, 20 (1997), pp. 445–450

31. F. Morabito, M. Martino, C. Stelitano, *et al.*

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

Haematologica, 87 (2002), pp. 1192–1199

32. F. Ferrara, S. Palmieri, A. Viola, *et al.*

Outpatient-based peripheral blood stem cell transplantation for patients with multiple myeloma

Hematol J, 5 (2004), pp. 222–226

33. M. Kassar, E. Medoff, S. Seropian, *et al.*

Outpatient high-dose melphalan in multiple myeloma patients

Transfusion, 47 (2007), pp. 115–119

34. M.A. Gertz, S.M. Ansell, D. Dingli, *et al.*

Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative

Mayo Clin Proc, 83 (2008), pp. 1131–1138

35. A. Gafter-Gvili, A. Fraser, M. Paul, *et al.*

Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy

Cochrane Database Syst Rev (1) (2012), p. CD004386 doi: 10.1002/14651858.CD004386.pub3

36. F. Fernandez-Aviles, E. Carreras, A. Urbano-Ispizua, *et al.*

Case-control comparison of at-home to total hospital care for autologous stem-cell transplantation for hematologic malignancies

J Clin Oncol, 24 (2006), pp. 4855–4861

37. A. Gafter-Gvili, A. Fraser, M. Paul, *et al.*

Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients

Ann Intern Med, 142 (2005), pp. 979–995

38. K.G. Moores

Safe and effective outpatient treatment of adults with chemotherapy-induced neutropenic fever

Am J Health Syst Pharm, 64 (2007), pp. 717–722

39. D. Capelli, G. Santini, C. De Souza, *et al.*

Amifostine can reduce mucosal damage after high-dose melphalan conditioning for peripheral blood progenitor cell autotransplant: a retrospective study

Br J Haematol, 110 (2000), pp. 300–307

40. H.V. Worthington, J.E. Clarkson, G. Bryan, *et al.*

Interventions for preventing oral mucositis for patients with cancer receiving treatment

Cochrane Database Syst Rev (2011), p. CD000978 doi: 10.1002/14651858.CD000978.pub5

41. J.R. Kouvaris, V.E. Kouloulias, L.J. Vlahos

Amifostine: the first selective-target and broad-spectrum radioprotector

Oncologist, 12 (2007), pp. 738–747

42.G.L. Phillips 2nd, S.H. Bernstein, J.L. Liesveld, *et al.*

A phase I trial: dose escalation of melphalan in the “BEAM” regimen using amifostine cytoprotection

Biol Blood Marrow Transplant, 17 (2011), pp. 1033–1042

43. P.D. Ziakas, I.S. Kourbeti

Pegfilgrastim vs. filgrastim for supportive care after autologous stem cell transplantation: can we decide?

Clin Transplant, 26 (2012), pp. 16–22