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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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A B S T R A C T

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.

INTRODUCTION

High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) [1,2] remains the standard of care for young medically fit patients with multiple myeloma (MM) [3-5]. Recent studies also suggest that induction therapy with so-called new drugs before transplantation may improve clinical outcomes [6,7]. In addition, long-term disease control can be achieved with a variety of post-transplantation consolidation [8] and maintenance therapies [9,10]. 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 [12,13]. 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].

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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 [15-17]. 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) [18,19], 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 $\leq .10$ 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).

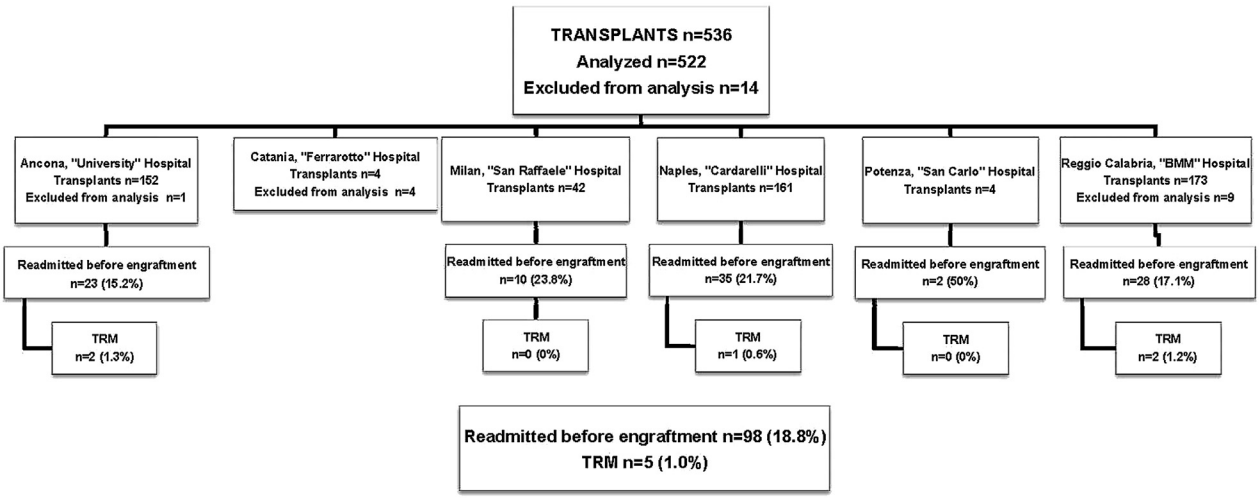

Figure 1. Retrospective Italian multicenter analysis of patients with multiple myeloma who underwent an autologous hemopoietic progenitor cell transplantation after an early discharge outpatient model between January 1998 and December 2012.