Strategies to upgrade safety for at-home autologous stem cell transplantation in multiple myeloma patients.

Luis Gerardo Rodríguez-Lobato (gerardo.lobato@gmail.com)  
Hospital Clínic de Barcelona  
https://orcid.org/0000-0001-5694-0921

Alexandra Martínez-Roca  
Hospital Clínic de Barcelona

Sandra Castaño-Díez  
Hospital Clínic de Barcelona

Alicia Palomino-Mosquera  
Hospital Clínic de Barcelona

Gonzalo Gutiérrez-García  
Hospital Clínic de Barcelona

Alexandra Pedraza  
Hospital Clínic de Barcelona

María Suárez-Lledó  
Hospital Clínic de Barcelona

Montserrat Rovira  
Hospital Clínic de Barcelona

Carmen Martínez  
Hospital Clínic de Barcelona

Carlos Fernández de Larrea  
Hospital Clínic de Barcelona

María Teresa Cibeira  
Hospital Clínic de Barcelona

Laura Rosiñol  
Hospital Clínic de Barcelona

Ester Lozano  
IDIBAPS

Pedro Marín  
Hospital Clínic de Barcelona

Joan Cid  
Hospital Clínic de Barcelona

Miquel Lozano  
Hospital Clínic de Barcelona
Research article

Keywords: neutropenic fever, multiple myeloma, transplantation, outpatient, engraftment syndrome

DOI: https://doi.org/10.21203/rs.3.rs-30978/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background. Autologous stem cell transplantation (ASCT) remains the standard of care for young multiple myeloma (MM) patients; indeed, at-home ASCT has been positioned as an appropriate therapeutic strategy. However, despite the use of prophylactic antibiotics, neutropenic fever (NF) and hospital readmissions continue to pose as the most important limitations in the outpatient setting. It is possible that the febrile episodes may have a non-infectious etiology, and engraftment syndrome could play a more significant role. The aim of this study was to analyze the impact of both G-CSF withdrawal and the addition of primary prophylaxis with corticosteroids after ASCT.

Methods. Between January 2002 and August 2018, 111 MM patients conditioned with melphalan were managed at-home beginning + 1 day after ASCT. Three groups were established: Group A (n = 33) received standard G-CSF post-ASCT; group B (n = 32) avoided G-CSF post-ASCT; group C (n = 46) avoided G-CSF yet added corticosteroid prophylaxis post-ASCT.

Results. The incidence of NF among the groups was reduced (64%, 44%, and 24%; \( P < 0.001 \)), with a non-significant decrease in hospital readmissions as well (12%, 6%, and 2%; \( P = 0.07 \)). The most important variables identified for NF were: HCT-CI > 2 (OR 6.1; \( P = 0.002 \)) and G-CSF avoidance plus corticosteroids (OR 0.1; \( P < 0.001 \)); and for hospital readmission: age \( \geq 60 \) years (OR 14.6; \( P = 0.04 \)) and G-CSF avoidance plus corticosteroids (OR 0.07; \( P = 0.05 \)).

Conclusions. G-CSF avoidance and corticosteroid prophylaxis post ASCT minimize the incidence of NF in MM patients undergoing at-home ASCT.

Introduction

The multiple myeloma (MM) treatment landscape has evolved dramatically over the last few years with the emergence of a next-generation proteasome inhibitor (carfilzomib), an immunomodulatory drug (pomalidomide) and monoclonal antibodies (daratumumab and elotuzumab) (1). However, most guidelines continue to support high-dose therapy followed by autologous stem cell transplantation (ASCT) as the standard of care for newly diagnosed patients without severe comorbidities (2–5). This treatment is considered a safe procedure with an extremely low transplant-related mortality (TRM) (< 3%), due to improvements that include the use of peripheral blood-derived hematopoietic stem cell products and post-transplantation administration of granulocyte colony-stimulating factor (G-CSF) (6, 7).

In recent years though, due to extensive waiting lists and an ever-growing concern about the proper use of health care resources, many groups have implemented outpatient ASCT programs. Such an approach has resulted in considerably acceptable outcomes in terms of hematopoietic recovery, toxicity and TRM; as well as improvements in cost and resource use, risk of infections, length of hospital admission and quality of life (8–12). Nevertheless, neutropenic fever (NF) continues to pose as the most important limitation in the outpatient setting with an estimated incidence of 80–100%, which in most cases acts as a main driver for hospital readmissions (8, 13–15). In light of such an observation, the use of antibiotic prophylaxis
during chemotherapy-induced neutropenia is recommended (16, 17). Since 2002, our group has enhanced infectious prophylaxis in the outpatient setting by adding ceftriaxone to levofloxacin, reducing the incidence of NF to 76% with a bacteremia rate of 26% and 8% in hospital readmissions (8). It is possible that the high incidence of NF in spite of antibiotic prophylaxis could be a consequence of non-infectious causes (18). Recently, the usefulness of G-CSF has been questioned; indeed, some transplant groups have stopped using it, observing no changes in relevant transplant outcomes and avoiding potential adverse effects including fatigue, bone pain, fever, engraftment syndrome (ES), and capillary leak syndrome (19, 20). In January 2011, our group too decided to follow suit and stop the routine use of G-CSF.

Engraftment syndrome is a syndromic entity occurring in the peri-engraftment period within the context of ASCT. It is characterized by non-infectious fever, skin rash, and diarrhea, resulting in less frequent hepatic dysfunction, transient encephalopathy, and capillary leak syndrome (21–23). While symptoms are usually mild and transient, some patients may, however, develop complications, delay hospital discharge, require intensive care treatment or experience death (24). The exact pathogenesis is not well understood; it is probable that the syndrome may arise in response to a release of pro-inflammatory cytokines (IL-2, TNF-α, IFN-γ, IL-8 and IL-6), associated with endothelial damage (high levels of vWF, sVCAM-1, sICAM-1, sTNFRI and low levels of ADAMTS-13 activity) and high levels of C-reactive protein (23–29). The estimated incidence of ES ranged between 5% and 72% (30, 31) depending on the diagnostic criteria implemented (21, 22). The onset of ES has been associated with ASCT for solid tumors (breast cancer), autoimmune diseases (multiple sclerosis) and monoclonal gammopathies (MM, AL amyloidosis and POEMS syndrome) that included the use of post-ASCT G-CSF, a high infused CD34+ cell dose, earlier and more rapid granulocyte recovery and the introduction of bortezomib and immunomodulatory drugs as induction therapy in MM (18, 23–26, 32–34). The most important aspect in managing ES is early recognition, ruling out alternative causes, and the use of corticosteroids (methylprednisolone 1 to 1.5 mg/Kg/day for two or three days) following a quick tapering regimen (26). Due to the dramatic response to corticosteroids, some authors have encouraged the pre-emptive or prophylactic use of such drugs (21, 31, 35). In observance of such aspect, our ASCT team established primary corticosteroid prophylaxis after ASCT in January 2014.

The aim of this study was to analyze the outcomes of different prophylactic policies to reduce NF, ES and hospital readmissions in our at-home ASCT program for patients with MM in order to increase the safety of those treatments by which these patients undergo. First: the standard G-CSF administration after ASCT; second: the withdrawal of G-CSF after ASCT; and third: the addition of primary prophylaxis for ES with corticosteroids after ASCT.

Materials And Methods

Patients

The clinical records of 853 consecutive ASCT for hematological malignancies at Hospital Clinic of Barcelona between January 2002 and August 2018 were reviewed. Patients who received ASCT in the in-patient setting were excluded (n=539). Two hundred and three patients were excluded for being non-MM
The final study population was comprised of 111 MM patients (Supplementary Figure 1). Some of the patients were included in a previous publication (18); however, the series has increased and only outpatients have been included in the analysis. The study was approved by the Ethics Committee of the Hospital Clínic of Barcelona, and was in accordance with the Declaration of Helsinki. The eligibility criteria for at-home transplantation included ECOG ≤ 2; travel time from home to the hospital <60 minutes; permanent caregiver availability. All patients signed an informed consent form.

**At-home ASCT program**

Our at-home ASCT program is based on the early-discharge outpatient model and has been published elsewhere (8,36). Data on prior induction treatment and peripheral stem cell mobilization regimen was collected. All patients received conditioning regimen with intravenous melphalan 200 mg/m$^2$; they were discharged from hospital the day after stem cell infusion. Hematology nurses visited patients once a day and performed laboratory tests three times a week. Prevention of chemotherapy-induced nausea and vomiting, and prophylaxis for oral mucositis (OM) followed standard international supportive care protocols. Red blood cell and platelet transfusion were administered when hemoglobin concentration was <8 g/dL and platelet count was ≤ 10 x 10$^9$/L, respectively. All patients received antimicrobial prophylaxis with fluoroquinolone, fluconazole, acyclovir (if herpes serology was positive), aerosolized pentamidine and enhanced antimicrobial prophylaxis with ceftriaxone (8) (1 g/day) from day +1 until the appearance of fever or neutrophil engraftment. At the onset of the first episode of NF, clinical evaluation, collection of blood and urine cultures and X-ray/CT scan were performed, along with empirical antimicrobial therapy with meropenem (1 g IV t.i.d.). Treatment with teicoplanin was added in cases when WHO grade ≥ 2 mucositis and signs of central venous access (CVA) infection existed. Empirical antimicrobial therapy was maintained until patients were afebrile for at least three days with no signs of infection and an absolute neutrophil count (ANC) of ≥ 1x10$^9$/L. When ES was suspected, methylprednisolone 1 mg/Kg/12h was administered for 3 days and then tapered over 7-8 days. Indications for hospital readmission were WHO grade 4 mucositis, uncontrolled vomiting or diarrhea, hemodynamic instability, respiratory distress, and willingness of caregiver or patient. At-home program discharge criteria consisted of an ANC of ≥ 1x10$^9$/L and afebrile status without antibiotic administration for a minimum of 48 hours.

**Prophylactic strategies to reduce neutropenic fever**

Patients were divided into three groups in the outpatient setting during three different time periods established in our transplant unit per the NF. Group A (January 2002 to December 2010) included all patients who received standard G-CSF (filgrastim) 5 mg/Kg/day beginning on post-transplant day +7 until ANC reached 1x10$^9$/L for three consecutive days; group B (January 2011 to December 2013) included patients who did not receive G-CSF post-transplant; and group C (January 2014 to August 2018) included patients who avoided G-CSF post-transplant, but did undergo primary prophylaxis with corticosteroids for
ES with oral prednisone 0.5 mg/Kg/day from day+7 until their ANC reached 0.5x10^9/L for three consecutive days.

**Definitions**

Neutrophil and platelet engraftment were defined as the first of three consecutive days, in which an ANC >0.5x10^9/L and platelet count >20x10^9/L without platelet transfusion were achieved, respectively. NF was defined as a newly observed temperature ≥38ºC with an ANC of <0.5x10^9/L and bacteremia as isolation of bacteria from a blood culture with fever or symptoms and/or signs of infection. ES was defined using Maiolino clinical criteria (21) (Table 1). Non-infectious fever was defined as a new fever without clinical or microbiological documentation or response to antimicrobials. Skin rash was defined as macular-papular exanthema mimicking acute graft versus host disease involving >25% of body surface area. Pulmonary infiltrates were considered secondary to ES in the absence of clinical and laboratory evidence of infection, cardiac failure, or pulmonary embolism. Diarrhea was defined as ≥2 episodes of liquid stool per day without microbiologically documented infection. Weight gain was defined >2.5% increase from baseline body weight. Hepatic and renal dysfunction was defined by either an elevation in serum bilirubin ≥2mg/dL or an increase in serum AST or ALT of ≥2 times the upper limit of normal (ULN) and serum creatinine of ≥2 times the ULN. Transient encephalopathy was defined as confusion not secondary to any other etiology.

**Statistical analysis**

Descriptive statistical analysis was performed. Median and range were used for continuous variables; meanwhile, frequency and percentage were used for categorical variables. Patient variables and outcomes were compared using Fisher’s exact test or c^2 test for categorical variables, as well as t-test or Wilcoxon rank-sum test for continuous variables. Univariate and multivariate binary logistic regression models were used to identify factors associated with NF, ES, and hospital readmission. Logistic regression analysis was performed by a backward stepwise method. The cumulative incidence of NF, ES, and hospital readmission were calculated with Gray’s test, as well as the Fine and Gray proportional hazard model for the analysis of the sub-distribution of competitive risks (37,38). The probability of progression-free survival (PFS) and overall survival (OS) was calculated with the Kaplan-Meier estimator; survival curves were compared with the log-rank test. The starting point for time-to-event analysis was the date of ASCT (39). All p values were two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed using R.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

**Results**

**Patient characteristics**
Patient demographics and clinical characteristics are summarized in Table 2. The median age was 56 years (range: 25-70) and 70 patients (63%) were males. As expected, the most frequent isotypes of heavy and light chain produced were IgG (49%) and Kappa (62%), respectively. Most patients had an International Staging System (ISS) of I (63%). Bortezomib-based schemes were received as an induction regimen in 84% of patients and 26% received ≥2 treatment lines before ASCT. The underlying disease was in complete response in 36% of the patients; meanwhile, 64% were in very good partial response or worse. Twenty-four patients (22%) had a hematopoietic cell transplantation-comorbidity index (HCT-CI) score of >2. The median infused CD34+ cell dose was 3.3 x 10^6/Kg (range, 1.7-9.4). Thirty-three patients (30%) received G-CSF post-ASCT (group A); 32 patients (29%) did not receive G-CSF post-ASCT (group B), and 46 patients (41%) avoided G-CSF post-ASCT and received primary prophylaxis with corticosteroids (group C). The groups were similar in most basal characteristics. However, we observed more ISS grade III patients in group C in comparison to group A (A: 6% vs. C: 19.5%; \( P=0.003 \)) and a greater number of patients in group B and C received bortezomib-based schemes (A: 58%, B: 91% and C: 98%; \( P<0.001 \)). Thirty-nine patients (39%) developed ES; their distributions according to symptoms were: fever (100%), diarrhea (86%), skin rash (28%), and pulmonary infiltrates (7%). The median follow-up of all patients was 39.8 months.

**Patient outcomes**

The most important clinical outcomes are summarized in Table 3. There was a significant difference in duration of severe neutropenia between patients that received G-CSF and those who did not, with a median of 8, 11, and 10 days in group A, B and C, respectively (A vs. B; \( P=0.005 \) and A vs. C; \( P=0.04 \)). The 10-day cumulative incidence of neutrophil engraftment was 88% (95% confidence interval [CI], 70-95%) in group A, 47% (95%CI, 26-62%) in group B, and 59% (95%CI, 42-71%) in group C (\( P=0.005 \)) (Figure 1). There were no differences among groups in either platelet engraftment or their requirement for platelet transfusions.

**Neutropenic fever**

There was a significant reduction in NF incidence between group A and group C (64% vs. 24%; \( P<0.001 \)), with a relative risk reduction of 0.38 (95%CI, 0.21-0.67; \( P<0.001 \)) and a number needed to treat of 2.52 (95%CI, 1.7-5.1). Onset and duration of NF were similar among groups. In the multivariate binary logistic regression analysis for NF, HCT-CI >2 was a risk factor (odds ratio [OR] 6.1; \( P=0.002 \)), while the avoidance of G-CSF and the addition of corticosteroids (group C) were protective (OR 0.1; \( P<0.001 \)) (Table 4). The 10-day cumulative incidence of NF were 61% in group A, 41% in group B, and 24% in group C (\( P=0.001 \)) (Figure 2A). In the competing risk regression model for NF, the avoidance of G-CSF and the addition of corticosteroids retained their independent protective factor (hazard ratio [HR] 0.53; \( P<0.001 \)) and HCT-CI >2 as risk factor (HR 2.24; \( P<0.01 \)). Regarding bacteremia, there were no differences in the number of positive blood cultures in all three groups (A: 2 isolations; B: 2 isolations; C: 1 isolation), and all were positive for
coagulase-negative *Staphylococcus*. During follow-up, there was a case of *Clostridioides difficile*-associated diarrhea in each two groups (A and C), which responded to oral vancomycin treatment.

Regarding the ES, its incidence decreased with the non-administration of G-CSF and the addition of prophylactic corticosteroids (group A: 58% vs, group C: 22%; *P*=0.001). The 10-day cumulative incidence of ES was 52% in group A, 38% in group B, and 17% in group C (*P*=0.002) (Figure 2B). In the multivariate analysis, the most important variables related to the development of ES were female gender (OR 2.3; *P*=0.05), HCT-CI >2 (OR 4.0; *P*=0.01), and group C (OR 0.2; *P*=0.02) (Table 4). The use of corticosteroids in group C did not increase the incidence of viral and fungal infections.

**Antibiotic use**

Patients who received G-CSF (Group A) and did not develop NF received fewer days of prophylactic antibiotic compared with Group B and C (A: 8 days; B: 11 days; C: 10 days; A vs. B or C; *P*<0.001) related to the duration of neutropenia. Respecting antibiotic treatment in patients who presented NF, Groups A and B received more days of antibiotic compared with group C (expressed in daily dose / outpatient-days) (meropenem: 0.3 vs. 0.2 vs. 0.09; *P*<0.001; teicoplanin: 0.09 vs. 0.08 vs. 0.02; *P*<0.001; amikacin: 0.04 vs. 0 vs. 0.004; *P*<0.001; Table 3).

**Toxicity and hospital readmission**

The non-administration of G-CSF with the addition of prophylactic corticosteroids did not modify the incidence and grade of mucositis, or other subtypes of toxicities including cutaneous, diarrhea, nausea, and vomiting (Table 3). Hospital readmission was necessary for four patients (12%) within group A, two patients (6%) within group B, and one patient (2%) within group C (A vs. C; *P*=0.07). The causes of readmissions were ES (n=3) and respiratory syncytial virus (RSV) pneumonia (n=1) in group A; ES (n=1) and RSV pneumonia in group B; and human metapneumovirus infection (n=1) in group C. In the multivariate analysis for hospital readmission, age ≥ 60 years was a risk factor (OR 14.6; *P*=0.04); meanwhile, the avoidance of G-CSF with the administration of corticosteroid retained an independent protective factor (OR 0.07; *P*=0.05) (Table 4).

**Transplant outcomes**

The one-year TRM in the whole series was 0.9% with no statistically significant differences among groups. The only death recorded occurred in group B on day +35 due to RSV pneumonia. There were no differences in PFS or OS between patients with and without NF, ES, and the avoidance of G-CSF with the
addition of corticosteroids. However, there was a substantial and expected improvement in group C PFS due to the use of novel drugs in the induction regimen (Figure 3A-D).

**Discussion**

This study demonstrates that patients with MM who received high-dose chemotherapy with melphalan and peripheral ASCT in the outpatient setting observe an increase in safely managing and reducing the incidence of NF. Such changes to support that conclusion include enhanced antibiotic prophylaxis with levofloxacin plus ceftriaxone; avoidance of G-CSF; and the addition of primary prophylaxis with corticosteroids after transplantation. The withdrawal of G-CSF and the use of corticosteroids did not increase the rate of infections nor did they modify transplant outcomes.

NF remains one of the most important concerns associated with ASCT in the outpatient setting. Despite the use of peripheral blood-derive hematopoietic stem cells and enhanced infectious prophylaxis, the incidence of NF and hospital readmissions in patients with MM remains high (30-80% and 8-33%, respectively) (11,14,15,40,41). Our group has incorporated the combination of levofloxacin plus ceftriaxone into the prophylactic antibiotic armamentarium, reducing the incidence of NF and hospital readmission to 76% and 8%, respectively (8). Trying to bolster at-home strategies to reduce these complications and assuming that febrile episodes may have a non-infectious etiology, we decided to withdraw the use of G-CSF and add corticosteroids after ASCT. Studies published 25 years ago that validate the use of G-CSF cannot be taken into account to support its use today; the value of growth factors must be reevaluated with current supportive care (19). In this study, the duration of severe neutropenia was longer in those groups who did not receive G-CSF post-ASCT, with a difference of two days. However, avoiding G-CSF did not modify the platelet engraftment, transfusion support, number of infections, or chemotherapy-related toxicity, which is consistent with other publications where the use of G-CSF is rationalized (18–20). The introduction of the two preventive measures (group C) led to a 90% decrease in odds for NF onset, entailing that 2.5 patients would need to avoid G-CSF and receive corticosteroids in order to reduce one episode of NF and make it a useful strategy in the outpatient setting. Risk factors associated with NF are diverse; nonetheless, in many series there is a strong correlation with older age, advanced stage disease, infusion of <5x10^6 CD34+/Kg, CVA infections, and OM (42). In this regard, the multivariate analysis revealed an HCT-CI >2 as risk factor, hinting that patients with greater number and severity of comorbidities are at greater risk of developing fever.

The incidence of ES in the group A of patients was 58% while in group C, it was 22%. Our new policy of G-CSF avoidance post-transplant and the use of primary prophylaxis with corticosteroids have remarkably reduced ES incidence. These results are consistent with those published by Mossad *et al.*, in which ES was reduced from 57% to 6% (31). Although the physiopathology of ES is not fully understood, it is possible that some pro-inflammatory risk factors for developing ES, such as older age, HCT-CI > 2 and pre-ASCT
treatment $\geq 2$ lines could be associated with the development of this complication (18). In contrast to other studies, we did not observe any association among the amount of infused CD34$^+$ cell dose, mobilization regimen, and use of novel anti-MM drugs in the development of ES.

The avoidance of G-CSF and the administration of corticosteroids did not boost the incidence of viral and fungal infections; it is likely due to the small variation in the number of days of severe neutropenia among groups and due to short use of corticosteroids. Regarding bacterial infections, the most frequently isolated bacteria was coagulase-negative *Staphylococcus* in all three groups, with these results being similar to those of other publications (12,43). Regarding *Clostridioides difficile*-associated diarrhea, we observed two cases, which agree with the 0 and 13% incidence rates published by other groups (8,12,14,15,43).

In terms of toxicity, the non-administration of G-CSF and the addition of corticosteroid did not modify the incidence and grade of OM, ratifying the importance of better oral health care and cryotherapy (44).

The observed hospital readmission rate was quite low in all groups. We were only able to observe a trend to reduce it in group C. It is difficult to carry out adequate comparisons with other published series, since the incidence of hospital readmission is very variable (8-87%), dependent on the model of outpatient transplant program, ECOG, comorbidities, subtype of hematological disease and proficiency of the at-home unit, among other elements (8,10–12,15).

This study has some limitations as a retrospective, non-randomized, single-center-based study. The study spans a long period and we could not assess the continuous improvement in supportive care and enhanced proficiency of physicians and nurses who care for these patients. However, patients in group C were older, with worse ISS, and had the same infused CD34$^+$ cell dose compared with group A. Notwithstanding, we observed a decrease in the incidence rate of NF and in hospital readmission, with no noted increase in adverse effects. We could not perform economic analysis; however, currently the median cost per day in our at-home ASCT program is €117, while the median hospital cost per day is €862, which represents important savings resulted mainly from lower hospitalization charges. Another benefit of our at-home transplant program is the ability to decrease the number of ward patients receiving an ASCT, and thus implement complex procedures, including haploidentical hematopoietic cell transplants and chimeric antigen receptor T-cells without increasing the number of hospital beds (45). Finally, the outpatient setting could become a potential approach to maintaining hematopoietic transplants during the COVID-19 pandemic.
In conclusion, this study suggests that for patients with multiple myeloma in at-home ASCT, the avoidance of G-CSF and the addition of primary prophylaxis with corticosteroids after ASCT minimize the incidence rates of NF and ES. This strategy does not compromise transplant outcomes or increase the infection rate. Notably, this preventive policy could provide clinicians with greater safety in the outpatient management of these patients.

**Declarations**

**Ethics approval and consent to participate.**

The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona and all patients signed a consent to participate.

**Consent for publication.**

Not applicable

**Availability of data and materials.**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests.**

The authors declare that they have no competing interests.

**Funding.**

The authors declare no financial disclosures

**Author’s contributions.**

LGRL, AMR and FFA designed the study; collected and analyzed data; performed statistical analysis; and wrote and reviewed the manuscript. SCD, APM, AP and EL collected data, as well as wrote and reviewed the paper. GGG, MSL, MR, CM, CFL, MTC, LR, PM, JC and ML treated patients and reviewed the paper. AM,
MP, MDR and EC collected, analyzed data, and reviewed the manuscript. CG, AH and SS were the nurses involved in the at-home unit. All authors approved the final version of the manuscript.

Acknowledgements.

Not applicable.

References

1. Cavo M, Terpos E, Bargay J, Einsele H, Cavet J, Greil R, et al. The multiple myeloma treatment landscape: international guideline recommendations and clinical practice in Europe. Expert Rev Hematol. 2018;11(3):219–37.

2. Ludwig H, Miguel JS, Dimopoulos MA, Palumbo A, Garcia Sanz R, Powles R, et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia. 2014 May;28(5):981–92.

3. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2017 Jul 1;28(suppl_4):iv52–61.

4. Sureda A, Bader P, Cesaro S, Dreger P, Duarte RF, Dufour C, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. Bone Marrow Transplant. 2015 Aug;50(8):1037–56.

5. Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2015 Nov;21(11):1863–9.

6. McCarthy PL, Hahn T, Hassebroek A, Bredeson C, Gajewski J, Hale G, et al. Trends in use of and survival after autologous hematopoietic cell transplantation in North America, 1995-2005: significant improvement in survival for lymphoma and myeloma during a period of increasing recipient age. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2013 Jul;19(7):1116–23.

7. Faussner F, Dempke WCM. Multiple myeloma: myeloablative therapy with autologous stem cell support versus chemotherapy: a meta-analysis. Anticancer Res. 2012 May;32(5):2103–9.

8. Fernández-Avilés F, Carreras E, Urbano-Ispizua A, Rovira M, Martínez C, Gaya A, et al. Case-control comparison of at-home to total hospital care for autologous stem-cell transplantation for hematologic
malignancies. J Clin Oncol Off J Am Soc Clin Oncol. 2006 Oct 20;24(30):4855–61.

9. Martino M, Lemoli RM, Girmenia C, Castagna L, Bruno B, Cavallo F, et al. Italian consensus conference for the outpatient autologous stem cell transplantation management in multiple myeloma. Bone Marrow Transplant. 2016 Aug;51(8):1032–40.

10. Faucher C, Le Corroller Soriano AG, Esterni B, Vey N, Stoppa AM, Chabannon C, et al. Randomized study of early hospital discharge following autologous blood SCT: medical outcomes and hospital costs. Bone Marrow Transplant. 2012 Apr;47(4):549–55.

11. Holbro A, Ahmad I, Cohen S, Roy J, Lachance S, Chagnon M, et al. Safety and cost-effectiveness of outpatient autologous stem cell transplantation in patients with multiple myeloma. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2013 Apr;19(4):547–51.

12. Graff TM, Singavi AK, Schmidt W, Eastwood D, Drobyski WR, Horowitz M, et al. Safety of outpatient autologous hematopoietic cell transplantation for multiple myeloma and lymphoma. Bone Marrow Transplant. 2015 Jul;50(7):947–53.

13. Piñana JL, Montesinos P, Martino R, Vazquez L, Rovira M, López J, et al. Incidence, risk factors, and outcome of bacteremia following autologous hematopoietic stem cell transplantation in 720 adult patients. Ann Hematol. 2014 Feb;93(2):299–307.

14. Satlin MJ, Vardhana S, Soave R, Shore TB, Mark TM, Jacobs SE, et al. Impact of Prophylactic Levofloxacin on Rates of Bloodstream Infection and Fever in Neutropenic Patients with Multiple Myeloma Undergoing Autologous Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2015 Oct;21(10):1808–14.

15. Lisenko K, Sauer S, Bruckner T, Egerer G, Goldschmidt H, Hillengass J, et al. High-dose chemotherapy and autologous stem cell transplantation of patients with multiple myeloma in an outpatient setting. BMC Cancer. 2017 22;17(1):151.

16. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2009 Oct;15(10):1143–238.

17. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011 Feb 15;52(4):e56-93.

18. Gutiérrez-García G, Rovira M, Magnano L, Rosiñol L, Bataller A, Suárez-Lledó M, et al. Innovative strategies minimize engraftment syndrome in multiple myeloma patients with novel induction therapy following autologous hematopoietic stem cell transplantation. Bone Marrow Transplant. 2018;53(12):1541–7.

19. Gertz MA, Gastineau DA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar SK, et al. SCT without growth factor in multiple myeloma: engraftment kinetics, bacteremia and hospitalization. Bone Marrow Transplant. 2011 Jul;46(7):956–61.

20. Cox JE, Campos S, Wu J, May R, Liu H, Ramos CA, et al. Efficacy of deferred dosing of granulocyte colony-stimulating factor in autologous hematopoietic transplantation for multiple myeloma. Bone
Marrow Transplant. 2014 Feb;49(2):219–22.

21. Maiolino A, Biasoli I, Lima J, Portugal AC, Pulcheri W, Nucci M. Engraftment syndrome following autologous hematopoietic stem cell transplantation: definition of diagnostic criteria. Bone Marrow Transplant. 2003 Mar;31(5):393–7.

22. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. Bone Marrow Transplant. 2001 May;27(9):893–8.

23. Carreras E, Fernández-Avilés F, Silva L, Guerrero M, Fernández de Larrea C, Martínez C, et al. Engraftment syndrome after auto-SCT: analysis of diagnostic criteria and risk factors in a large series from a single center. Bone Marrow Transplant. 2010 Sep;45(9):1417–22.

24. Spitzer TR. Engraftment syndrome: double-edged sword of hematopoietic cell transplants. Bone Marrow Transplant. 2015 Apr;50(4):469–75.

25. Dispenzieri A, Lacy MQ, Hayman SR, Kumar SK, Buadi F, Dingli D, et al. Peripheral blood stem cell transplant for POEMS syndrome is associated with high rates of engraftment syndrome. Eur J Haematol. 2008 May;80(5):397–406.

26. Cornell RF, Hari P, Drobyski WR. Engraftment Syndrome after Autologous Stem Cell Transplantation: An Update Unifying the Definition and Management Approach. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2015 Dec;21(12):2061–8.

27. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. Bone Marrow Transplant. 2011 Dec;46(12):1495–502.

28. Palomo M, Diaz-Ricart M, Carbo C, Rovira M, Fernandez-Aviles F, Escolar G, et al. The release of soluble factors contributing to endothelial activation and damage after hematopoietic stem cell transplantation is not limited to the allogeneic setting and involves several pathogenic mechanisms. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2009 May;15(5):537–46.

29. Palomo M, Diaz-Ricart M, Carbo C, Rovira M, Fernandez-Aviles F, Martine C, et al. Endothelial dysfunction after hematopoietic stem cell transplantation: role of the conditioning regimen and the type of transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2010 Jul;16(7):985–93.

30. Gale RP, Lazarus HM. Engraftment syndrome, the Emperor’s new clothes and the artist formerly known as Prince. Bone Marrow Transplant. 2015 Apr;50(4):483–4.

31. Mossad S, Kalaycio M, Sobecks R, Pohlman B, Andresen S, Avery R, et al. Steroids prevent engraftment syndrome after autologous hematopoietic stem cell transplantation without increasing the risk of infection. Bone Marrow Transplant. 2005 Feb;35(4):375–81.

32. Cornell RF, Hari P, Zhang M-J, Zhong X, Thompson J, Fenske TS, et al. Divergent effects of novel immunomodulatory agents and cyclophosphamide on the risk of engraftment syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2013 Sep;19(9):1368–73.

33. Martínez-Cibrian N, Magnano L, Gutiérrez-García G, Andrade X, Correa JG, Suárez-Lledó M, et al. At-home autologous stem cell transplantation in multiple myeloma with and without G-CSF...
administration: a comparative study. Bone Marrow Transplant. 2016 Apr;51(4):593–5.

34. Gutiérrez-García G, Cibeira MT, Rovira M, Fernández de Larrea C, Tovar N, Rodríguez-Lobato LG, et al. Improving security of autologous hematopoietic stem cell transplant in patients with light-chain amyloidosis. Bone Marrow Transplant. 2019 Aug;54(8):1295–303.

35. Openshaw H, Nash RA, McSweeney PA. High-dose immunosuppression and hematopoietic stem cell transplantation in autoimmune disease: clinical review. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2002;8(5):233–48.

36. Rodríguez-Lobato LG, Martínez-Roca A, Moreno DF, Gutiérrez-García G, Suárez-Lledó M, Rovira M, et al. Impact of intensifying primary antibiotic prophylaxis in at-home autologous stem cell transplantation program for lymphoma patients. Leuk Lymphoma. 2020 Mar 25;0(0):1–10.

37. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. Bone Marrow Transplant. 2007 Aug;40(4):381–7.

38. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. Bone Marrow Transplant. 2010 Sep;45(9):1388–95.

39. Delgado J, Pereira A, Villamor N, López-Guillermo A, Rozman C. Survival analysis in hematologic malignancies: recommendations for clinicians. Haematologica. 2014 Sep;99(9):1410–20.

40. Paul TM, Liu SV, Chong EA, Luger SM, Porter DL, Schuster SJ, et al. Outpatient Autologous Stem Cell Transplantation for Patients With Myeloma. Clin Lymphoma Myeloma Leuk. 2015 Sep;15(9):536–40.

41. Martino M, Russo L, Martinello T, Gallo GA, Fedele R, Moscato T, et al. A home-care, early discharge model after autografting in multiple myeloma: results of a three-arm prospective, non-randomized study. Leuk Lymphoma. 2015 Mar;56(3):801–4.

42. Eleutherakis-Papaiakovou E, Kostis E, Migkou M, Christoulas D, Terpos E, Gavriatopoulou M, et al. Prophylactic antibiotics for the prevention of neutropenic fever in patients undergoing autologous stem-cell transplantation: results of a single institution, randomized phase 2 trial. Am J Hematol. 2010 Nov;85(11):863–7.

43. Solano C, Gutierrez A, Martinez F, Gimeno C, Gómez C, Muñoz I, et al. Prophylaxis of early bacterial infections after autologous peripheral blood stem cell transplantation (PBSCT): a matched-pair study comparing oral fluoroquinolones and intravenous piperacillin-tazobactam. Bone Marrow Transplant. 2005 Jul;36(1):59–65.

44. Marchesi F, Tendas A, Giannarelli D, Viggiani C, Gumenyuk S, Renzi D, et al. Cryotherapy reduces oral mucositis and febrile episodes in myeloma patients treated with high-dose melphalan and autologous stem cell transplant: a prospective, randomized study. Bone Marrow Transplant. 2017;52(1):154–6.

45. Gutiérrez-García G, Rovira M, Arab N, Gallego C, Sánchez J, Ángeles Álvarez M, et al. A reproducible and safe at-home allogeneic haematopoietic cell transplant program: first experience in Central and Southern Europe. Bone Marrow Transplant. 2020 May;55(5):965–73.

**Abbreviations**

ADAMTS-13 A disintegrin-like and metalloprotease with thrombospondin type 1 motif 13
ANC  Absolute neutrophil count
ASCT  Autologous stem cell transplantation
CI    Confidence interval
CR    Complete response
COVID-19 Coronavirus disease 2019
CVA   Central venous access
ECOG  Eastern Cooperative Oncology Group
ES    Engraftment syndrome
G-CSF Granulocyte colony-stimulating factor
HCT–CI Hematopoietic cell transplantation–comorbidity index
HR    Hazard ratio
IFN-g Interferon gamma
IL-2  Interleukin 2
IL-6  Interleukin 6
IL-8  Interleukin 8
ISS   International Staging System
IV    Intravenous
MM    Multiple myeloma
MR    Minimal response
NF    Neutropenic fever
OM    Oral mucositis
OR    Odds ratio
OS    Overall survival
PFS   Progression-free survival
PO | Oral
---|---
POEMS | Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes
PR | Partial response
RSV | Respiratory syncytial virus
sICAM-1 | Soluble intercellular adhesion molecule-1
sTNFRI | Soluble tumor necrosis factor receptor-1
sVCAM-1 | Soluble vascular cell adhesion molecule-1
TNF-a | Tumor necrosis factor alpha
TRM | Transplant-related mortality
ULN | Upper limit of normal
VGPR | Very good partial response
vWF | Von Willebrand factor
WHO | World Health Organization

### Tables

**Table 1. Clinical criteria for engraftment syndrome diagnosis**

| Maiolino criteria for engraftment syndrome |
|-------------------------------------------|
| Non-infectious fever plus one of the following: |
| Skin rash |
| Pulmonary infiltrates |
| Diarrhea¹ |

¹ At least two episodes of liquid depositions/day without microbiological documentation of infection. Starting 24h before or at any time after the first appearance of neutrophils.

---

**Table 2. Main patient characteristics.**
| Characteristic                      | Total group (n=111) | Group A (n=33) | Group B (n=32) | Group C (n=46) | P      |
|-----------------------------------|---------------------|----------------|----------------|----------------|--------|
|                                  |                     |                |                |                | A vs. B | B vs. C | A vs. C |
| Age (range)                       | 56 (25-70)          | 51 (25-67)     | 57 (40-69)     | 58 (39-70)     | 0.03   | 0.71    | 0.06    |
| Gender, male (%)                  | 70 (63)             | 20 (61)        | 18 (56)        | 32 (69.6)      | 0.72   | 0.23    | 0.41    |
| Immunological subtype             |                     |                |                |                |        |         |         |
| IgG (%)                           | 54 (49)             | 17 (52)        | 18 (56)        | 19 (41.3)      | 0.89   | 0.36    | 0.85    |
| IgA (%)                           | 29 (26)             | 8 (24)         | 9 (28)         | 12 (26.1)      | 0.06   | 0.71    | 0.23    |
| Bence Jones (%)                   | 25 (23)             | 7 (21)         | 5 (16)         | 13 (28.4)      |        |         |         |
| Light chain isotype, Kappa (%)    | 69 (62)             | 19 (58)        | 17 (53)        | 33 (71.7)      | 0.71   | 0.14    | 0.23    |
| ISS                               |                     |                |                |                | 0.55   | 0.04    | 0.003   |
| I (%)                             | 70 (63)             | 27 (82)        | 23 (72)        | 20 (43.5)      |        |         |         |
| II (%)                            | 28 (25)             | 4 (12)         | 7 (22)         | 17 (37.09)     |        |         |         |
| III (%)                           | 13 (12)             | 2 (6)          | 2 (6)          | 9 (19.5)       |        |         |         |
| Number of pre-ASCT lines ≥ 2 (%)  | 29 (26)             | 8 (24)         | 8 (25)         | 13 (28.3)      | 1.00   | 0.8     | 0.8     |
| Pre-transplant therapy            | 18 (16)             | 14 (42)        | 3 (9)          | 1 (2.2)        | 0.002  | 0.16    | <0.001  |
| Chemotherapy (%)                  | 93 (84)             | 19 (58)        | 29 (91)        | 45 (97.8)      |        |         |         |
| Bortezomib-based schemes (%)      |                     |                |                |                |        |         |         |
| Response before ASCT              |                     |                |                |                |        |         |         |
| CR (%)                            | 40 (36)             | 15 (46)        | 8 (25)         | 17 (37.0)      | 0.23   | 0.53    | 0.64    |
| VGPR / PR (%)                     | 65 (59)             | 16 (49)        | 22 (69)        | 27 (58.7)      |        |         |         |
| MR / progression (%)              | 6 (5)               | 2 (5)          | 2 (6)          | 2 (4.3)        |        |         |         |
| Mobilization                      |                     |                |                |                |        |         |         |
| G-CSF (%)                         | 92 (83)             | 31 (94)        | 26 (82)        | 35 (76)        | 0.20   | 0.10    | 0.08    |
| G-CSF + cyclophosphamide (%)      | 5 (5)               | 2 (6)          | 3 (9)          | 0 (0)          |        |         |         |
| Plerixafor (%)                    | 14 (12)             | 0 (0)          | 3 (9)          | 11 (24)        |        |         |         |
| HCT-CI >2 (%)                     | 24 (22)             | 4 (12)         | 8 (25)         | 12 (26.1)      | 0.18   | 0.91    | 0.13    |
| CD34⁺ x10⁹/Kg (range)             | 3.3 (1.7-9.4)       | 3.2 (1.9-6.4)  | 3.0 (1.9-9.4)  | 3.6 (1.7-7.2)  | 0.57   | 0.51    | 0.14    |

Group A: G-CSF without corticosteroids; Group B: No G-CSF without corticosteroids; Group C: No G-CSF adding corticosteroids.

ASCT: autologous stem cell transplantation; CR: complete response; HCT-CI: hematopoietic cell transplantation-comorbidity index; ISS: international staging system; MR: minimal response; PR: partial response; VGPR: very good partial response.
Table 3. Clinical outcomes.
| Characteristics                                                                 | Group A (n=33) | Group B (n=32) | Group C (n=46) | P       |
|-------------------------------------------------------------------------------|----------------|----------------|----------------|---------|
| **Engraftment**                                                              |                |                |                | A vs. B | B vs. C | A vs. C |
| First day of neutropenia ≤ 0.5x10^9/L (range)                                 | 4 (0-5)        | 4 (1-5)        | 4 (3-6)        | 0.31    | 0.07    | 0.009   |
| Duration of neutropenia ≤ 0.5x10^9/L (range)                                 | 8 (5-22)       | 11 (6-18)      | 10 (7-21)      | **0.005** | 0.24    | **0.04** |
| Duration of thrombocytopenia ≤ 20,000x10^3/L (range)                          | 12 (0-37)      | 12 (9-17)      | 11 (0-34)      | 0.37    | 0.58    | 0.27    |
| **Fever**                                                                    |                |                |                |         |         |         |
| Neutropenic fever (≥38°C) (%): First day with fever (range)                   | 21 (64)        | 14 (44)        | 11 (24)        | 0.11    | 0.07    | **0.0004** |
| Duration of fever (range)                                                     | 7.5 (4-12)     | 8 (3-11)       | 8 (5-9)        | 0.47    | 0.34    | 0.75    |
| Positive blood cultures (%)                                                   | 2 (1-5)        | 1 (1-5)        | 3 (1-5)        | 0.09    | **0.05** | 0.56    |
| **Engraftment syndrome**                                                      |                |                |                |         |         |         |
| Fever (%)                                                                     | 19 (58)        | 14 (44)        | 10 (22)        | 0.27    | **0.04** | **0.001** |
| Rash (%)                                                                      | 19 (100)       | 14 (100)       | 10 (100)       |         |         |         |
| Diarrhea (%)                                                                  | 5 (26)         | 4 (29)         | 3 (30)         |         |         |         |
| Pulmonary infiltrates (%)                                                     | 15 (79)        | 12 (86)        | 10 (100)       |         |         |         |
| **Antibiotic use**                                                            |                |                |                |         |         |         |
| Days with antibiotic prophylaxis, median (range): Without further presence of fever | 8 (5-11) | 11 (6-16) | 10 (7-21) | <0.001 | 0.44 | <0.001 |
| Meropenem daily dose / outpatient-days*                                        | 4 (0-9)        | 4 (0-8)        | 4 (0-6)        | 0.18    | 0.23    | 0.79    |
| Teicoplanin daily dose / outpatient-days*                                       | 0.3            | 0.2            | 0.09           | <0.001  | <0.001  | <0.001  |
| Amikacin daily dose / outpatient-days*                                         | 0.09           | 0.08           | 0.02           | 0.56    | <0.001  | <0.001  |
| Further presence of fever, Days with antibiotic treatment                     | 0.04           | 0           | 0.004          | <0.001  | 0.27    | <0.001  |
### Toxicity

| Toxicity                           | (%) | (%) | (%) | (%) | (%) | (%) |
|------------------------------------|-----|-----|-----|-----|-----|-----|
| Mucositis ≥ 2                     | 2 (6)| 0 (0)| 2 (4)| 0.49| 0.51| 1.00|
| Cutaneous ≥ 2                      | 0 (0)| 0 (0)| 0 (0)| 1.00| 1.00| 1.00|
| Diarrhea ≥ 2                      | 1 (3)| 0 (0)| 9 (20)| 1.00| 1.00| 0.08|
| Nausea and vomiting ≥ 2 (%)        | 0 (0)| 0 (0)| 1 (2)| 1.00| 1.00| 1.00|

### Hospital readmission

| Readmissions (%) | Duration of readmission (range) |
|------------------|---------------------------------|
| 4 (12)           | 8 (4-13)                       |
| 2 (6)            | 2.5 (2-39)                     |
| 1 (2)            | 12                              |

* Total sum of antibiotic days in the sample / total sum of days of sample follow-up.

**Table 4. Multivariate regression model for neutropenic fever, engraftment syndrome, and hospital readmission.**

| Characteristic                      | OR  | 95% CI       | P    |
|-------------------------------------|-----|--------------|------|
| **Neutropenic fever**               |     |              |      |
| Gender, female                      | 1.8 | 0.7-4.6      | 0.2  |
| HCT-CI > 2                          | 6.1 | 1.9-19.4     | 0.002|
| No G-CSF with corticosteroid        | 0.1 | 0.02-0.4     | 0.0007|
| **Engraftment syndrome**            |     |              |      |
| Gender, female                      | 2.3 | 0.9-5.6      | 0.07 |
| HCT-CI > 2                          | 4.0 | 1.4-11.4     | 0.01 |
| No G-CSF with corticosteroid        | 0.2 | 0.1-0.8      | 0.02 |
| **Hospital readmission**            |     |              |      |
| Age ≥ 60 years                      | 14.6| 1.1-19.9     | 0.04 |
| No G-CSF with corticosteroid        | 0.07| 0.01-0.99    | 0.05 |

**Figures**

Page 21/25
Figure 1

Cumulative incidence of neutrophil engraftment comparing group A (G-CSF without corticosteroid), group B (avoiding G-CSF and corticosteroid), group C (avoiding G-CSF and adding corticosteroid) during the first 30 days after autologous stem cell transplantation.
Figure 2

A. Cumulative incidence of neutropenic fever comparing group A (G-CSF without corticosteroid), group B (avoiding G-CSF and corticosteroid), group C (avoiding G-CSF and adding corticosteroid) during the first 30 days after autologous stem cell transplantation. B. Cumulative incidence of engraftment syndrome comparing group A (G-CSF without corticosteroid), group B (avoiding G-CSF and corticosteroid), group C (avoiding G-CSF and adding corticosteroid) during the first 30 days after autologous stem cell transplantation. C. Cumulative incidence of hospital readmission comparing group A (G-CSF without corticosteroid), group B (avoiding G-CSF and corticosteroid), group C (avoiding G-CSF and adding corticosteroid) during the first 30 days after autologous stem cell transplantation.
Figure 3

A. Progression-free survival comparing group A, group B, and group C; B. Progression-free survival in all patients with and without engraftment syndrome; C. Overall survival comparing group A, group B, and group C; D. Overall survival in all patients with and without engraftment syndrome.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.pdf