A prospective, multicenter study on hematopoietic stem-cell mobilization with cyclophosphamide plus granulocyte colony-stimulating factor and 'on-demand' plerixafor in multiple myeloma patients treated with novel agents

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Abstract

High-dose melphalan plus autologous stem cell transplantation (ASCT) is a standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM), and adequate hematopoietic stem cell (HSC) collection is crucial to ensure hematologic recovery after ASCT. In this prospective, observational study we evaluated HSC mobilization with granulocyte colony-stimulating factor (G-CSF), cyclophosphamide, and 'on-demand' plerixafor (in patients with $<20\times10^6$ CD34$^+$ cells/L after at least 4 days of G-CSF or failing to collect $\geq1\times10^6$ CD34$^+$ cells/kg after the first apheresis) in NDMM patients treated with novel agent-based induction therapy. The primary endpoint was the rate of poor mobilizers (patients collecting $<2\times10^6$ CD34$^+$ cells/kg or requiring plerixafor rescue to reach an adequate HSC harvest). Secondary endpoints included the rate of patients collecting $\geq2\times10^6$ CD34$^+$ cells/kg after plerixafor administration and the identification of factors predicting mobilization failure or plerixafor need. Overall, 301 patients (median age 60 years) were enrolled. Two hundred and eighty-seven of 301 (95%) and 274 of 301 (93%) patients collected $\geq2\times10^6$ and $\geq4\times10^6$ CD34$^+$ cells/kg, respectively, with a

median of 9.9×10^6 CD34$^+$ cells/kg collected. Poor mobilizers were 48 of 301 (16%): 34 of 301 (11%) required plerixafor rescue, and 14 of 301 (5%) failed HSC collection regardless of plerixafor. Thirty-four of 38 (90%) patients receiving plerixafor collected ≥2×10^6 CD34$^+$ cells/kg. Bone marrow plasmacytosis at diagnosis >60% (odds ratio [OR]=4.14), lenalidomide use (OR=4.45), and grade 3-4 hematologic toxicities during induction (OR=3.53) were independently associated with a higher risk of mobilization failure or plerixafor need. Cyclophosphamide plus G-CSF and 'on-demand' plerixafor is an effective strategy in NDMM patients treated with novel agents, resulting in a high rate of HSC collection and high HSC yield (*clinicaltrials gov. identifier: NCT03406091*).

Introduction

Treatment intensification with high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT) after multi-drug, novel agent-based induction therapy currently represents the standard of care for transplant-eligible (TE) patients with newly diagnosed multiple myeloma (NDMM).[1] Based on the results of the randomized, phase III STAMINA and EMN02/HO95 studies, tandem autologous transplant can be offered to patients with high-risk cytogenetics.[1-3] At relapse, salvage ASCT proved to be beneficial when incorporated into a novel agent-based salvage strategy and is therefore a potential option for patients who experienced a prolonged remission after upfront ASCT.[4,5] The hematologic recovery after myeloablative chemotherapy depends on the dose of stem cell progenitors infused, while the minimum collection goal to ensure adequate bone marrow (BM) recovery is 2×10^6 CD34$^+$ cells/kg for a single transplant. Therefore, a collection goal of at least 4-5×10^6 CD34$^+$ cells/kg is necessary to proceed to ASCT and ensure the possibility of a tandem transplant in high-risk patients or a salvage transplant at relapse.[1,6]

Standard stem cell mobilization strategies include steady-state mobilization with granulocyte colony-stimulating factor (G-CSF) only or conventional chemotherapy (mainly cyclophosphamide 2-4 g/m^2) plus G-CSF.[7,8] Despite the use of both strategies, up to 15-20% of NDMM patients fail to collect a minimum number of hematopoietic stem cells (HSC) to proceed to ASCT.[7]

Plerixafor is a CXC chemokine receptor 4 (CXCR4) antagonist that prompts the release of HSC from the BM in the peripheral blood (PB) by disrupting the interaction between CXCR4 and chemokine stromal cell-derived factor-1α (SDF-1α). Plerixafor is approved for HSC mobilization in MM and lymphoma patients, as it demonstrated to increase the efficiency of HSC mobilization, with a higher CD34$^+$ cell yield, lower failure rates, and a reduced number of aphereses.[9,10] Approximately 50-70% of NDMM patients who underwent mobilization with G-CSF only, and 10-20% of patients who underwent chemo-mobilization required the use of plerixafor for successful HSC collection.[11-15] The wide use of novel agents such as lenalidomide and anti-CD38 monoclonal antibodies (mAb; e.g., daratumumab and isatuximab) during the induction phase may impact stem cell collection.[16] A French study showed that the use of plerixafor was four times higher with the administration of lenalidomide upfront, as compared with thalidomide.[17] Furthermore, a recent analysis of the MASTER and GRIFFIN trials showed that the incorporation of daratumumab into induction treatment resulted in an approximately 2-fold increase in the rate of patients requiring plerixafor, as compared with daratumumab-free regimens.[18]

Different strategies concerning the use of plerixafor for stem cell mobilization have been developed and adopted by different institutions, from its 'on-demand' or 'just-in-time' use (plerixafor administered according to a risk-adapted strategy based on either the number of PB CD34$^+$ cells before the apheresis or the first CD34$^+$ stem cell yield)[19-21] to a 'pre-emptive' strategy in patients at high risk of stem-cell mobilization failure.[18]

Data regarding the efficacy of plerixafor as rescue medication during HSC mobilization with chemotherapy plus G-CSF in the era of novel agents are limited, and few prospective studies, mainly conducted before the implementation of lenalidomide and anti-CD38 mAb in the induction treatment of NDMM patients, have systematically assessed factors influencing HSC mobilization.

Here we present the results of a prospective, multicenter, observational study conducted to evaluate HSC mobilization with cyclophosphamide plus G-CSF and 'on-demand' plerixafor in NDMM patients treated with novel agent-based induction regimens and to identify predictive factors for poor mobilization and the need for plerixafor administration.

Methods

Study design and participants

MOZOBL06877 (*clinicaltrials gov. identifier: NCT03406091*) is a multicenter, prospective, observational study conducted in 17 Italian centers between November 2015 and January 2021. This study enrolled TE NDMM patients aged 18 years or older, who received induction therapy containing novel agents, and underwent HSC mobilization with cyclophosphamide (2-4 g/m^2) plus G-CSF (5-10 mcg/kg/day) and 'on-demand' plerixafor as per local policy. Patients with relapsed and/or refractory (RR) MM, patients who underwent mobilization with chemotherapy other than cyclophosphamide or with G-CSF only, and patients who had failed a previous mobilization attempt were not eligible for

enrollment in this study.

We collected data on baseline patient and disease characteristics (including age, sex, MM isotype and stage, cytogenetic risk detected by fluorescent *in situ* hybridization [FISH], percentage of BM plasma cells, BM function, and renal function), type and duration of induction therapy, response rates and grade 3-4 hematologic adverse events (AE) during the induction phase, and time to stem cell mobilization. We also collected details concerning mobilization strategy, number of PB $CD34^+$ cells on the first day of counting and before and after plerixafor administration, total number of $CD34^+$ harvested cells, number of apheresis days, plerixafor use (number of administrations, dose delivered, reasons for administration), and occurrence of AE during the mobilization phase and up to 30 days after the end of apheresis.

The study protocol was approved by the independent ethics committees or institutional review boards at each of the participating centers. All patients gave written, informed consent before participating in the study, which was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline. This study is registered as *clinicaltrials gov. identifier: NCT03406091*.

Stem cell mobilization and harvesting

HSC were mobilized with intravenous cyclophosphamide at the dose of 2-4 g/m^2 at day 0, followed by G-CSF at 5-10 mcg/kg/day starting from day +5 until the end of HSC harvesting. According to the label and institutional practice, 'on-demand' plerixafor could be administered in patients with $<20\times10^6$ $CD34^+$ cells/L after at least 4 consecutive days of G-CSF or in patients failing to collect $\geq1\times10^6$ $CD34^+$ cells/kg after the first apheresis day. Plerixafor was administered at the dose of 240 mcg/kg/day (or 160 mcg/kg/day in case of renal impairment) as a subcutaneous injection 6-11 hours prior to the initiation of the subsequent apheresis, for up to 5 days until the HSC harvest target was reached. Collection failure was defined as a $CD34^+$ stem cell collection $<2\times10^6$ $CD34^+$ cells/kg.

Endpoints: definition and assessment

The primary endpoint was to determine the rate of poor-mobilizing patients, defined as the rate of patients collecting $<2\times10^6$ $CD34^+$ cells/kg or who required 'on-demand' plerixafor to reach an adequate HSC harvest. Secondary endpoints included the rate of patients who collected $\geq2\times10^6$ or $\geq4\times10^6$ $CD34^+$ cells/kg overall, with and without 'on-demand' plerixafor; the rate of patients who received 'on-demand' plerixafor; the HSC collection 'rescue rate' of plerixafor, defined as the rate of patients receiving plerixafor who collected $\geq2\times10^6$ $CD34^+$ cells/kg; the increase in the levels of $CD34^+$ cells after plerixafor administration; the number of $CD34^+$ cells/kg collected per apheresis with and without plerixafor; the identification of factors predicting a poor mobilization and the need for plerixafor administration; and the rate of grade 3-4 non-hematologic AE during mobilization.

Statistical analysis

All enrolled patients who underwent HSC mobilization with cyclophosphamide plus G-CSF and 'on-demand' plerixafor were included in this analysis. Discrete variables were reported as numbers and percentages. Continuous variables were summarized using median and interquartile range (IQR). The Fisher's exact test was adopted to compare categorical variables and the Kruskal-Wallis test to compare continuous variables between groups.

A univariate analysis of factors associated with poor mobilization was performed. Starting from the variables with a *P* value (*P*)<0.05 in univariate analysis, a multivariate logistic model was identified through a backward selection based on the minimization of the Akaike information criterion. The final logistic regression model was used to estimate odds ratios (OR), 95% confidence intervals (CI), and *P*. All reported *P* were two-sided; the conventional value of 5% was adopted as significance level.

High-risk cytogenetics were defined as the presence of at least one of the following cytogenetic abnormalities detected by FISH: del(17p), t(4;14), or t(14;16).[22] Disease assessment at the end of the induction phase was evaluated according to the International Myeloma Working Group response criteria.[23] Incidence, categories, and severity of AE were reported according to the Common Terminology Criteria for Adverse Events Version 4.0. Cytopenia at diagnosis was defined as at least one of the following values: hemoglobin <10 g/dL, absolute neutrophil count (ANC) $<1\times10^9$/L, or platelets $<100\times10^9$/L. Data were analyzed using R (Version 4.2.1).[24]

Results

Patient characteristics

Between November 2015 and January 2021, 303 TE NDMM patients were enrolled in this study, 301 of whom underwent HSC mobilization with cyclophosphamide at 2-4 g/m^2 plus G-CSF and were included in the analysis. Two patients were excluded from the analysis: one due to disease progression before HSC mobilization, and one because HSC was performed with G-CSF only, thus not meeting the inclusion criteria for enrollment.

The median age at diagnosis was 60 years (IQR, 55-64), and 142 patients (47%) were older than 60 years of age (Table 1). Among the evaluable patients (N=224), 59 (26%) had Revised International Staging System (R-ISS) stage I disease, 151 (67%) R-ISS II, and 14 (6%) R-ISS III. High-risk cytogenetic abnormalities were detected in 43 of 158 (27%) patients with available FISH data. At diagnosis, the median value of BM plasma cells was 50% (IQR, 29-70%),

Table 1. Patient demographics and baseline characteristics.

	N=301
Age in years	
Median (IQR)	60 (55-64)
≤60, N (%)	159 (53)
>60, N (%)	142 (47)
Sex, N (%)	
Female	131 (44)
Male	170 (56)
Isotype, N (%)	
IgG	191 (64)
IgA	62 (21)
Bence–Jones	33 (11)
Other	13 (44)
Missing	2
Bone marrow plasma cells %	
Median % (IQR)	50 (29-70)
≤60, N (%)	183 (65)
>60, N (%)	97 (35)
Missing, N	21
ISS stage, N (%)	
I	174 (58)
II	83 (28)
III	44 (15)
R-ISS stage, N (%)	
I	59 (26)
II	151 (67)
III	14 (6)
Missing	77
Cytogenetic risk assessed by FISH, N (%)	
Standard	115 (73)
High*	43 (27)
Missing	143
Cytopenia at diagnosis**, N (%)	
No	255 (85)
Yes	44 (15)
Missing	2

*High risk was defined as the presence of del(17p) or t(4;14) or t(14;16). **Cytopenia was defined as Hb <10 g/dL or ANC <1×10^9/L or PLT <100x10^9/L. ANC: absolute neutrophil count; del, deletion; FISH, fluorescence *in situ* hybridization; Hb: hemoglobin; IQR: interquartile range; ISS: International Staging System; PLT:, platelets; R-ISS: Revised International Staging System; t: translocation.

with >60% in 35% of patients <100×10^9/L.

The majority of patients received bortezomib-based induction therapy (N=266, 88%), mostly bortezomib-thalidomide-dexamethasone (VTd; N=241, 80%; Table 2). Lenalidomide was part of the induction regimen in 29 patients (10%), carfilzomib in 21 (7%), and daratumumab in ten (3%). Patients received a median number of five induction cycles (IQR, 4-6) before proceeding to HSC mobilization. At the end of the induction phase, 79 patients (27%) achieved a partial response (PR), 167 (56%) a very good partial response (VGPR), and 47 (16%) a complete response (CR) or better. Twenty-seven patients (9%) experienced ≥1 grade 3-4 hematologic toxicities during induction.

The median time from diagnosis to stem cell mobilization was 6 months (IQR, 5-8), while the median time from the end of induction to cyclophosphamide administration was 30 days (IQR, 20-47).

Before mobilization, the median values of ANC, hemoglobin, and platelets were 3.1×10^9/L (IQR, 2.34-4.32), 12.9 g/dL (IQR, 11.9-13.6), and 238.5×10^9/L (IQR, 204-295.75), respectively.

Cyclophosphamide was administered at the dose of 2 g/m^2 in 144 patients (48%), 3 g/m^2 in 73 (24%), and 4 g/m^2 in 84 (28%).

Patient characteristics, induction details, and response rates before HSC mobilization are summarized in Table 2.

Hematopoietic stem cell mobilization

Overall, 287 of 301 (95%) patients collected ≥2×10^6 CD34$^+$ cells/kg, 253 (84%) without plerixafor administration, while 34 (11%) with 'on-demand' plerixafor administration (Figure 1).

Fourteen of 301 (5%) patients failed to collect ≥2×10^6 CD34$^+$ cells/kg; among them, four (1%) received 'on-demand' plerixafor, while ten (4%) did not. Regarding the primary endpoint, 48 patients (16%) were considered poor mobilizers: 14 (5%) due to HSC mobilization failure (HSC collection <2×10^6 CD34$^+$ cells/kg) and 34 (11%) due to the need for 'on-demand' plerixafor.

'On-demand' plerixafor was administered to 38 patients (13%): to 25 due to a pre-apheresis count of <20×10^6 CD34$^+$ cells/L and to 13 due to a CD34$^+$ stem-cell yield <1×10^6/kg after the first apheresis. The median number of plerixafor doses administered was 1 (range, 1-3). Thirty-five (92%) patients received 0.24 mg/kg of plerixafor, while three (8%) received 0.16 mg/kg.

Among patients who received plerixafor, 34 of 38 successfully collected ≥2×10^6 CD34$^+$ cells/kg, while four of 38 failed HSC mobilization, resulting in an overall 'HSC collection rescue rate' of 90%.

Overall, patients collected a median of 9.9×10^6 CD34$^+$ cells/kg (IQR, 7.7-12.8); the median HSC yield was 10.2×10^6 CD34$^+$ cells/kg (IQR, 8.3-13.2) in patients who did not require plerixafor and 6.5×10^6 CD34$^+$ cells/kg (IQR, 4.6-9.6) in those who received 'on-demand' plerixafor.

Among patients who did not require plerixafor (N=253), 244 (95%) collected >4×10^6 CD34$^+$ cells/kg, while eight (5%) collected between 2×10^6 and 4×10^6 CD34$^+$ cells/kg. In the plerixafor group (N=34), 30 (88%) patients collected >4×10^6 CD34$^+$ cells/kg, while four (12%) between 2×10^6 and 4×10^6 CD34$^+$ cells/kg. Patients who received lenalidomide-based (N=23) or daratumumab-based (N=10) induction regimens collected a median of 6.4×10^6 and 9.75×10^6 CD34$^+$ cells/kg, respectively. Poor mobilizers were respectively ten (43%) and four (40%) in the lenalidomide and daratumumab groups, of whom seven (30%) and four (40%) required plerixafor administration, while three (13%) and none failed to collect ≥2×10^6 CD34$^+$ cells/kg in the two groups, respectively.

As expected, among patients who successfully collected

Table 2. Induction treatment, disease response, and patient characteristics before hematopoietic stem cell mobilization.

	N=301
Induction regimen, N (%)	
VTd	241 (80)
VRd	4 (1)
KRd	20 (7)
KCd	1 (1)
DVRd	7 (2)
DVCd	3 (1)
Other bortezomib-based regimens*	25 (8)
N of induction cycles	
Median (IQR)	5 (4-6)
≤4, N (%)	148 (49)
>4, N (%)	151 (51)
Missing, N	2
Response after induction, N (%)	
ORR	293 (99)
≥VGPR	214 (72)
sCR/CR	47 (16)
VGPR	167 (56)
PR	79 (27)
SD	3 (1)
PD	1 (<1)
Missing	4
Grade 3-4 hematologic toxicity during induction, N (%)	
No	273 (91)
Yes	27 (9)
Missing	1
Pre-mobilization ANC	
Median (IQR) $\times 10^9$/L	3.1 (2.34-4.32)
<2.5x10^9/L N (%)	10 (3)
≥2.5x10^9/L N (%)	281 (97)
Missing, N	10
Pre-mobilization Hb	
Median (IQR) g/dL	12.9 (11.9-13.6)
<12 g/dL N (%)	78 (27)
≥12 g/dL N (%)	216 (73)
Missing, N	7
Pre-mobilization PLT count	
Median (IQR) $\times 10^9$/L	238.5 (204-295.75)
<150x10^9/L N (%)	14 (5)
≥150x10^9/L N (%)	280 (95)
Missing, N	7
Cyclophosphamide dose, N (%)	
2 g/m^2	144 (48)
3 g/m^2	73 (24)
4 g/m^2	84 (28)

*This group includes unspecified bortezomib-based regimens, such as the following regimens: Vd (bortezomib-dexamethasone), VCd (bortezomib-cyclophosphamide-dexamethasone), and PAD (bortezomib-doxorubicin-dexamethasone). ANC: absolute neutrophil count; CR: complete response; DVCd: daratumumab-bortezomib-cyclophosphamide-dexamethasone; DVRd: daratumumab-bortezomib-lenalidomide-dexamethasone; Hb: hemoglobin; IQR, interquartile range; KCd, carfilzomib-cyclophosphamide-dexamethasone; KRd: carfilzomib-lenalidomide-dexamethasone; ORR: overall response rate; PD: progressive disease; PLT: platelets; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response; VRd: bortezomib-lenalidomide-dexamethasone; VTd: bortezomib-thalidomide-dexamethasone.

HSC (N=287), the median number of $CD34^+$ cells/L on the first day of counting was higher in those who did not require plerixafor (70.9×10^6; IQR, 33.7-124.6), as compared with those rescued with 'on-demand' plerixafor (16×10^6; IQR, 7-29.5). However, an approximately 3-fold increase in the median number of $CD34^+$ cells/L was observed after plerixafor administration, from 17.5×10^6 (IQR, 10.8-27.6) to 58.3×10^6 (IQR, 34.2-100.2) $CD34^+$ cells/L.

The median number of aphereses was 1 (IQR, 1-2) in patients who did not require plerixafor and 2 (IQR, 1-2) in the 'on-demand' plerixafor group, while the median number of $CD34^+$ cells/kg collected per apheresis with and without plerixafor was 7.06×10^6 $CD34^+$ cells/kg (IQR, 4.64-11.3) in patients who did not require plerixafor and 3.5×10^6 $CD34^+$ cells/kg (IQR, 2.15-5.3) in patients rescued with plerixafor. The main outcomes of HSC mobilization and collection are summarized in Table 3.

Predictors of poor mobilization

In univariate analysis, baseline BM plasmacytosis >60% of total BM cells (OR=3.96, 95% CI: 2.0-7.7; *P*<0.001), lenalidomide-based induction regimens (OR=5.48, 95% CI: 2.43-12.36; *P*<0.001), daratumumab-based induction regimens (OR=6.31, 95% CI: 2.74-15.5; *P*=0.03), occurrence of a grade 3-4 hematologic toxicity during induction (OR=6.31, 95% CI: 2.74-14.54; *P*<0.001), low pre-mobilization ANC <2.5×10^9/L (OR=2.78, 95% CI: 1.49-5.26; *P*=0.001), and hemoglobin levels <12 g/dL (OR=2.08, 95% CI: 1.09-4; *P*=0.03) were associated with an increased risk of mobilization failure or the need for plerixafor administration (*Online Supplementary Table S1* in the *Online Supplementary Appendix*). In multivariate analysis, BM plasmacytosis >60% of total BM cells (OR=4.14, 95% CI: 1.98–8.67; *P*<0.001), lenalidomide-based induction regimens (OR=4.45, 95% CI: 1.69-11.72; *P*=0.002), and occurrence of a grade 3-4 hematologic toxicity during induction (OR=3.53, 95% CI: 1.32-9.44; *P*=0.012) were independently associated with a higher risk of mobilization failure or the need for plerixafor administration. Patients exposed to daratumumab showed a trend of being at higher risk of mobilization failure, although not statistically significant in multivariate analysis (OR=2.17, 95% CI: 0.39-12.11; *P*=0.37; Table 4).

Safety of hematopoietic stem cell mobilization

Overall, during the observation period, 16 (5%) patients experienced any-grade, non-hematologic AE, of which the most frequent ones were bone pain (2%), nausea and vomiting (1%), and infections (2%), while worsening/exacerbation of peripheral neuropathy was reported in 1% of patients. Only two (1%) patients experienced a grade 3 infection. No grade 4-5 AE were observed. No differences in the rates of AE were observed between patients who received plerixafor and those who did not (*Online Supplementary Table S2*).

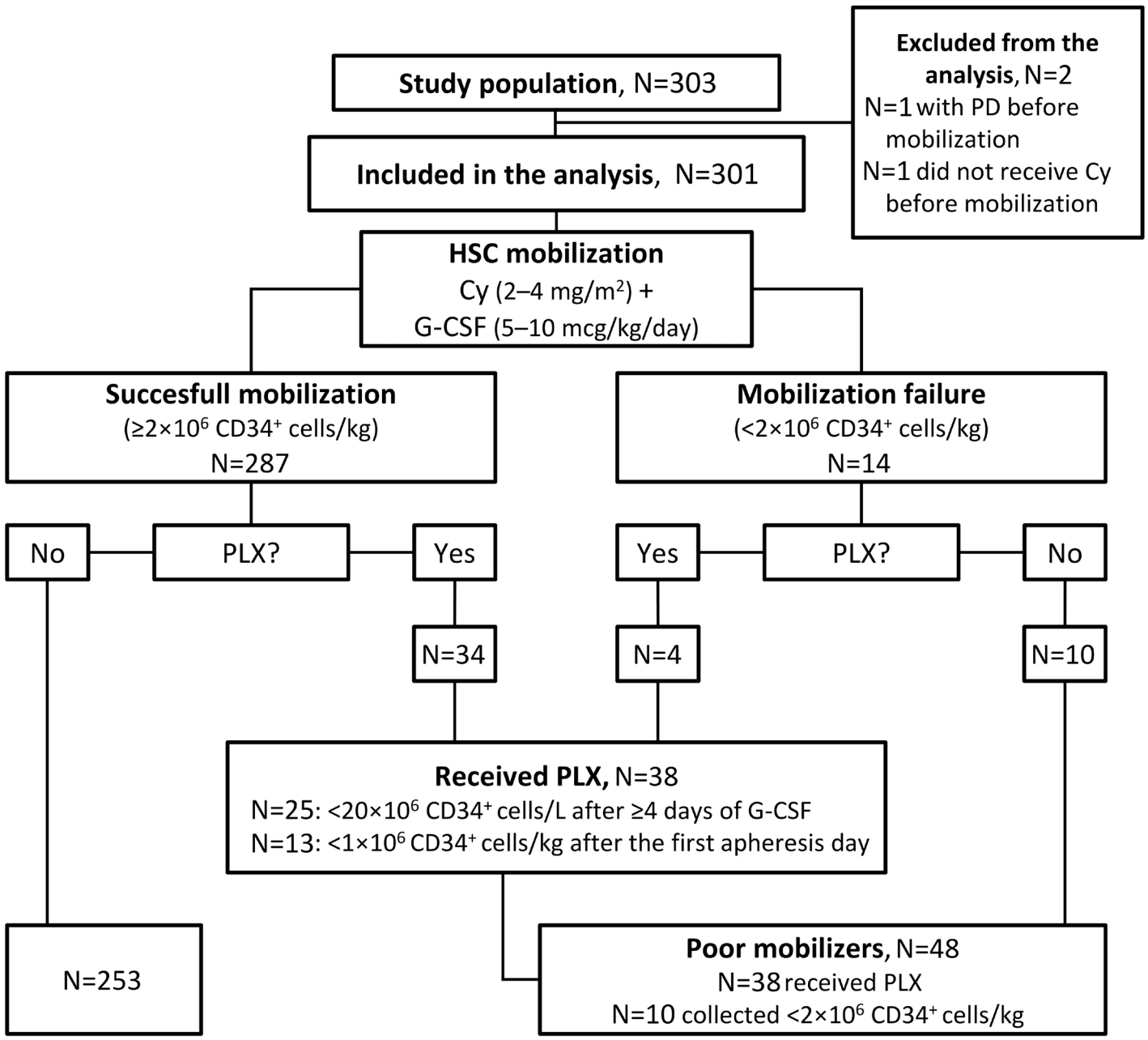

Figure 1. Study flowchart. Cy: cyclophosphamide; G-CSF: granulocyte colony-stimulating factor; HSC: hematopoietic stem cell; PD: progressive disease; PLX: plerixafor.

Discussion

In the era of multi-drug, novel agent-based induction regimens, HDM followed by ASCT remains a standard approach for TE patients. Currently, tandem autologous transplant is recommended by the EHA-ESMO guidelines in patients with high-risk disease and is being investigated in clinical trials enrolling high-risk patients,[25] while salvage transplant at relapse is recommended in patients with a long duration of remission from a prior transplant.[1] In this light, an optimal collection of autologous HSC is essential to allow patients to proceed to a single or double transplant, in compliance with the initial treatment plan and in order to preserve the possibility of a salvage transplant at relapse. HSC mobilization strategies have evolved over time and currently include a steady-state approach with G-CSF alone or in combination with chemotherapy (e.g., high-dose cyclophosphamide), with plerixafor administered either pre-emptively in patients with a high risk of stem cell mobilization failure or as a rescue drug in those who have failed to meet the stem cell target. As induction therapies for TE NDMM patients have rapidly evolved, with the incorporation of agents that can potentially impact stem cell mobilization (e.g., the immunomodulatory agent lenalidomide and the mAb targeting CD38 daratumumab), the efficiency of stem cell mobilization strategies and their ability to meet the optimal CD34⁺ target need to be reassessed.

In this large, prospective study we evaluated 301 patients treated with novel agent-based triplets and quadruplets (including lenalidomide, carfilzomib, and daratumumab) who underwent stem cell mobilization with cyclophosphamide (2-4 g/m²) plus G-CSF and 'on-demand' plerixafor, to assess the risk of poor mobilization, the need for plerixafor administration, and its efficacy as a rescue agent. This mobilization strategy resulted in a high rate (95%) of patients who successfully collected HSC at first attempt. The need for plerixafor administration, either due to a low CD34⁺ cell count before apheresis or a low HSC yield after the first day of collection, was low (11% of the overall population), and 'on-demand' plerixafor confirmed to be a highly effective rescue strategy, allowing a successful HSC collection in 90% of patients receiving it.

Before the availability of plerixafor, the rate of mobilization failures in MM patients undergoing chemotherapy-based mobilization varied between 5% and 40%.[15,16,26-31] In a large study of 1,384 MM patients enrolled in different clinical tri-

Table 3. Mobilization and harvesting outcomes in patients with successful hematopoietic stem-cell collection.

Parameters	Mobilizing patients N=287	Patients without plerixafor administration N=253	Patients with plerixafor administration N=34
$CD34^+ \times 10^6$ cells/L on the first count day Median (IQR)	60.05 (25.4-112.8)	70.9 (33.7-124.6)	16 (7-29.5)
$CD34^+ \times 10^6$ cells/L before plerixafor administration Median (IQR)	-	-	17.5 (10.75-25.6)
$CD34^+ \times 10^6$ cells/L after plerixafor administration Median (IQR)	-	-	58.3 (34.2-100.2)
Total of $CD34^+ \times 10^6$ cells/kg Median (IQR) Suboptimal collection,* N of pts (%) Optimal collection,** N of pts (%)	 9.9 (7.7-12.8) 12 (4) 274 (96)	 10.2 (8.3-13.2) 8 (3) 244 (97)	 6.5 (4.6-9.6) 4 (12) 30 (88)
N of apheresis days 1 day, N of pts (%) 2 days, N of pts (%) 3 days, N of pts (%) 4 days, N of pts (%)	 155 (55) 102 (36) 20 (7) 4 (1)	 142 (57) 86 (35) 15 (6) 4 (2)	 13 (38) 16 (47) 5 (15) 0
HSC collection per apheresis day*** Median (IQR) $CD34^+$ cells/kg $\times 10^6$	6.5 (4.3-10.79)	7.06 (4.64-11.3)	3.5 (2.15-5.3)

*Suboptimal collection: total HSC collected 2-4×10^6 $CD34^+$ cells/kg. **Optimal collection: total HSC collected over 4×10^6 $CD34^+$ cells/kg. ***HSC collection per apheresis day was assessed as the median of total $CD34^+$ cells collected per apheresis session. IQR: interquartile range; pts: patients; HSC: hematopoietic stem cell.

Table 4. Multivariate model for predictors of hematopoietic stem cell mobilization failure or plerixafor use.

Parameters	OR (95% CI)	*P*
Bone marrow PC at diagnosis, >60% *vs.* ≤60%	4.14 (1.98-8.67)	<0.001
Lenalidomide-based induction, yes *vs.* no	4.45 (1.69-11.72)	0.002
Daratumumab-based induction, yes *vs.* no	2.17 (0.39-12.11)	0.37
Grade 3-4 hematologic toxicity during induction, yes *vs.* no	3.53 (1.32-9.44)	0.012
Pre-mobilization ANC, <2.5x10^9/L *vs.* ≥2.5x10^9/L	1.92 (0.91-4)	0.081
Pre-mobilization Hb, <12 g/dL *vs.* ≥12 g/dL	1.92 (0.91-4)	0.084

ANC: absolute neutrophil count; CI: confidence interval; OR: odds ratio; PC: plasma cells; Hb: hemoglobin.

als and mobilized with cyclophosphamide (3-4 g/m^2) plus G-CSF, Musto *et al.* reported a mobilization failure rate of 21%, including 12.4% of patients failing to collect ≥2×10^6 $CD34^+$ cells/kg and 8.4% with a sub-optimal collection (2-5×10^6 $CD34^+$ cells/kg).[16]

Dugan *et al.* published a first report regarding the safety and efficacy of plerixafor plus chemotherapy and G-CSF in 44 patients with MM and non-Hodgkin lymphoma.[32] The addition of plerixafor to various chemotherapy regimens and G-CSF led to a median 2-fold increase in the number of circulating $CD34^+$ cells and to an increase in the HSC yield. Our results confirmed the efficacy of 'on-demand' plerixafor in rescuing patients at high risk of mobilization failure, limiting its rate to 5% and therefore comparing favorably to the data reported by Musto *et al.*[16]

Our study also confirmed the results of a retrospective study by Johnsrud *et al.* of 398 MM patients undergoing HSC mobilization with either cyclophosphamide (4 g/m^2) plus G-CSF or G-CSF alone and 'on-demand' plerixafor.[15] The mobilization failure rate was approximately 5% in both groups, and the rate of patients requiring plerixafor in the cyclophosphamide group (12%) was similar to that in our study (11%). Of note, in our study, compared to that by Johnsrud *et al.*, we observed similar rates of patients

who collected ≥2×10^6 CD34$^+$ cells/kg (95% in both studies) or >4×10^6 CD34$^+$ cells/kg (90% and 94%, respectively) and of plerixafor administration (11% and 12%), despite a lower average dose of cyclophosphamide in our study. These results are clinically meaningful, as higher doses of cyclophosphamide are associated with higher rates of febrile neutropenia.[33,34]

A steady-state mobilization with G-CSF is an effective and appealing strategy compared with a chemotherapy-based approach, particularly due to the availability of plerixafor. Retrospective and prospective studies showed the feasibility and efficacy of HSC mobilization with G-CSF only plus 'on-demand' plerixafor in MM patients receiving 3-4 drug induction regimens.[15,18]

The proportion of patients who successfully collected the minimum number of HSC required to proceed to ASCT was similar in our study (95%) and in the phase II GRIFFIN and MASTER trials (94% and 100%), where patients received G-CSF only plus plerixafor.[15,18] However, the median stem cell yields obtained with G-CSF only in the GRIFFIN (8.3×10^6 CD34$^+$ cells/kg) and MASTER (6×10^6 CD34$^+$ cells/kg) studies were lower than that obtained in our study with cyclophosphamide plus G-CSF (9.9×10^6 CD34$^+$ cells/kg), and fewer patients in the GRIFFIN (85%) and MASTER (80%) studies achieved an optimal collection of HSC than in our study (90%), despite a significantly higher use of plerixafor than in our study (72% and 97% *vs.* 11%). Although cross-study comparisons are limited by differences in induction treatments and collection goals, the results observed with cyclophosphamide and G-CSF in our study compared favorably with those observed with G-CSF only in terms of stem cell yield, optimal collection rates, and days of apheresis and plerixafor administration, thus providing an effective mobilization option for patients in whom a high HSC yield is planned (e.g., in case of tandem or salvage transplant) or for those who are at high risk of mobilization failure due to the presence of multiple risk factors.

We evaluated baseline and premobilization factors that could potentially be associated with a higher risk of mobilization failure or the need for plerixafor administration in the context of a cyclophosphamide plus G-CSF mobilization. In our study, BM infiltration >60% at diagnosis (OR=4.14), the occurrence of grade 3-4 hematologic toxicities during induction (OR=3.53), and lenalidomide-based induction (OR=4.45) were independently associated with a higher risk of mobilization failure or the need for plerixafor administration. Lenalidomide-based induction therapy was correlated with a negative impact on HSC collection in several studies,[15-17,35,36] and the results of our study confirmed this evidence.

Randomized clinical studies investigating standard induction triplets with or without the anti-CD38 mAb daratumumab in NDMM patients showed higher use of plerixafor and lower stem cell yields in patients receiving daratumumab, regardless of the mobilization strategy adopted.[37] In the phase III CASSIOPEIA study, patients underwent HSC mobilization with cyclophosphamide and G-CSF: a higher use of plerixafor (22% *vs.* 8%) and lower HSC yields (6.7×10^6 *vs.* 10×10^6 CD34$^+$ cells/kg) were observed in the daratumumab *versus* non-daratumumab arms.[12] Similarly, in the phase II GRIFFIN trial, in which a steady-state mobilization with G-CSF plus either upfront or rescue plerixafor was adopted, higher rates of plerixafor administration (72% *vs.* 55%) and lower HSC yields (8.3×10^6 *vs.* 9.4×10^6 CD34$^+$ cells/kg) were observed in the daratumumab *versus* non-daratumumab arms. In both trials, however, >95% patients were able to proceed to and complete ASCT. In line with these results, in our study upfront daratumumab was associated with a higher risk of mobilization failure or need for plerixafor administration (OR=2.17), although this was not statistically significant in multivariate analysis, possibly due to the small number of patients in the daratumumab group. To account for this limitation and further investigate the impact of daratumumab on HSC mobilization, a retrospective study comparing the efficacy and efficiency of stem cell collection with G-CSF plus 'on-demand' plerixafor in a large series of patients treated with or without daratumumab is currently ongoing.

In our study, we did not observe new safety concerns associated with 'on-demand' plerixafor administration. The rate of grade 3-4 AE was low (1%), possibly because the majority of patients (72%) received intermediate doses of cyclophosphamide (2-3 g/m^2), which have already been associated with a lower risk of AE compared with higher doses. These data also confirm the safety of such mobilization strategy.[21]

A limitation of this study is the lack of data regarding transplantation and engraftment. However, several studies compared engraftment outcomes in patients whose HSC were collected with or without plerixafor, showing no differences in terms of engraftment, neutrophil recovery, and platelet recovery in both groups.[9,10,15]

In conclusion, we confirmed that HSC mobilization with cyclophosphamide plus G-CSF and 'on-demand' plerixafor is an effective mobilization strategy also in the era of novel agent-based induction treatments (including lenalidomide, carfilzomib, and daratumumab), resulting in a high rate of successful HSC collection and high HSC yields.

Disclosures

RM has received honoraria from Janssen, Celgene, Takeda, and Amgen; has served on advisory boards for Janssen, Celgene, Takeda, Bristol Myers Squibb, Amgen, and Pfizer; has received consultancy fees from Janssen, Takeda, and Sanofi. MTP has received honoraria from and served on the advisory boards for Celgene–Bristol Myers Squibb, Janssen-Cilag, Takeda, Amgen, Sanofi, GlaxoSmithKline, Pfizer, and Menarini. RS has received honoraria from Novartis, Gilead, and Mallinckrodt. RML has served on advisory boards for Stemline, Menarini, and Jazz Pharma. SB has received

honoraria from Bristol Myers Squibb, Sanofi, and Janssen. FF has received honoraria from Janssen-Cilag, Takeda, Amgen, and GlaxoSmithKline. KM has received honoraria from Celgene, Takeda, Amgen, Sanofi, and Janssen. During the past 3 years, PC has received honoraria (for consultancy, participation in advisory role, or lectures) from AbbVie, ADC Therapeutics (DSMB), Amgen, Celgene, Daiichi Sankyo, Gilead/Kite, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin, Nerviano Medical Science, Novartis, Pfizer, Roche, Sanofi, SOBI, and Takeda; has received support for travel and accomodation from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Gilead/Kite, Janssen, Novartis, Roche, and Takeda. MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, and AbbVie; has served on advisory boards for Janssen and GlaxoSmithKline; has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, and Mundipharma. All other authors have no conflicts of interest to disclose.

Contributions

RM, FB, BB, and MB substantially contributed to the conception and design of this article. All authors substantially contributed to the acquisition, analysis, or interpretation of data for this article and accessed and verified the underlying data. RM, FB, and GB drafted this article. All authors reviewed this article critically for important intellectual content. All authors finally approved the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data-sharing statement

After the publication of this article, data collected for this analysis and related documents (including the study protocol) will be made available to others upon reasonably justified request, which needs to be written and addressed to the attention of the corresponding author. The sponsor of the MOZOBL06877 study, the Foundation European Myeloma Network (EMN) Italy ONLUS (Torino, Italy), via the corresponding author, is responsible to evaluate and eventually accept or refuse every request to disclose data and their related documents, in compliance with the ethical approval conditions, in compliance with applicable laws and regulations, and in conformance with the agreements in place with the involved subjects, the participating institutions, and all the other parties directly or indirectly involved in the participation, conduct, development, management and evaluation of this analysis.

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