Impact of daratumumab/bortezomib/thalidomide and dexamethasone induction therapy on chemo-free stem cell mobilization in transplant-eligible newly diagnosed multiple myeloma: a multicenter real-world experience

Transplant-eligible newly diagnosed multiple myeloma (TE-NDMM) patients are currently treated with quadruplet induction therapy including the anti-CD38 monoclonal antibody daratumumab followed by one or two courses of high-dose melphalan and autologous stem cell transplantation (ASCT).[1] The mobilization of peripheral blood stem cells is crucial for the successful performance of the transplant program and it can be accomplished using conventional chemotherapy, most frequently cyclophosphamide (2-4 g/m^2) combined with granulocyte colony-stimulating factor (G-CSF), or a chemo-free therapy with G-CSF alone, with or without plerixafor.[2,3]

Recently, with the widespread use of anti-CD38 monoclonal antibodies (daratumumab, isatuximab) during the induction phase, there has been growing concern about the mobilization of peripheral blood stem cells. Although there is not a clear understanding of the underlying mechanism, many authors speculate that in patients treated with anti-CD38$^+$ monoclonal antibodies, leukocytes, stromal cells, or endothelial cells overexpress adhesive molecules negatively affecting mobilization.[4]

Regardless of the mobilization strategy adopted, data from the largest randomized clinical trials comparing daratumumab-based regimens showed a higher use of plerixafor, more leukaphereses and lower stem cell yields in patients receiving daratumumab. Nevertheless, in all trials, most patients underwent the planned ASCT.[5-7] The impact of daratumumab on stem cell mobilization has recently been reported in retrospective real-life studies.[8-13]

In this large observational, multicenter, retrospective study, we analyzed TE-NDMM patients given quadruplet induction therapy with daratumumab, bortezomib, thalidomide and dexamethasone and mobilized with a chemo-free strategy (G-CSF and plerixafor on demand) at two Italian centers. The study was approved by the Territorial Ethics Committee of Sicily (Italy) and is registered with EudraCT number 1199 (17/4/2024).

The purpose of the study was to assess the efficacy of the mobilization, particularly with regard to the mobilization failure rate, number of CD34$^+$ cells harvested and the need for plerixafor administration. From January 2022 to January 2024, 100 patients with TE-NDMM were included. The diagnosis and response were defined according to International Myeloma Working Group criteria.[14]

The target stem cell mobilization was 2.0x10^6 cells/kg for one ASCT and 4x10^6 cells/kg for two ASCT. According to our institutional mobilization protocol, patients received subcutaneous G-CSF 10 μg/day from day +1. CD34$^+$ cell count was first determined at day +5 and leukapheresis was started if there were more than 20 CD34$^+$ cells/μL and continued for 1 to 4 days until the target was achieved. Plerixafor 240 μg/kg was administered on demand 6-11 hours before apheresis if the circulating CD34$^+$ cell count was less than 20/μL at day +5. A CD34$^+$ cell yield <2.0×10^6/kg was considered as failure. Patients who failed chemo-free mobilization underwent a second chemo-based strategy to harvest stem cells. The chemotherapy consisted of cyclophosphamide (2 g/m^2) and high-dose cytarabine (1,600 mg/m^2) plus G-CSF 5 μg/day from day +6. The conditioning regimen consisted of high-dose melphalan (200 mg/m^2 or 140 mg/m^2 in the case of renal impairment or age ≥65 years). Stem cells were infused the day after (considered as day 0) through a central vein access.

Data collection was approved by the local ethics committee and all patients provided written informed consent.

The statistical analysis was performed using R studio version 4.1.2. Categorical variables were reported as counts with percentages and continuous variables as medians with ranges. χ^2 tests were used to compare categorical variables. A univariate analysis of factors associated with mobilization failure (yes *vs*. no), plerixafor use (yes *vs*. no), days of leukapheresis (≤1 *vs*. >1) and number of CD34$^+$ cells (<4x10^6/kg *vs*. ≥4x10^6/kg) was performed. The final logistic regression model was used to estimate odds ratios, 95% confidence intervals, and *P* values.

The patients' baseline characteristics are reported in Table 1. One hundred patients with a median age of 61 years (range, 42-71) were included. The median number of induction cycles was four (range, 3-6). Responses to induction were complete response (16%), very good partial response (60%), partial response (16%), stable disease (1%) and unknown (7%). The patients flow through the mobilization procedure is reported in Figure 1.

Peripheral blood stem cells were mobilized in 63% of patients after four cycles and in 37% after three cycles. The median time from last daratumumab infusion to the start of G-CSF was 25 days (range, 9-109). Overall, peripheral blood stem cell harvest after the first chemo-free mobilization was

successful in 90% of patients: in 58/90 (64%) an optimal stem cell harvest was obtained after G-CSF alone, while plerixafor on demand was added in 31/90 patients (36%). Seventy-seven of the 90 patients (86% of patients) whose peripheral blood stem cells were successfully mobilized yielded more than $4x10^6$/kg $CD34^+$ cells.

In the cohort mobilized with G-CSF alone (N=58), the median peak $CD34^+$ cell count was 58/μL (range, 16-490) and the median of $CD34^+$ cells harvested was $6.2x10^6$/kg (range, 1.3-23.9), with 49/58 (84%) patients yielding more than $4×10^6$/kg. The median number of aphereses was two (range, 1-3).

In the cohort mobilized with the addition of plerixafor on demand (N=31), the median peak $CD34^+$ cell count was 48.5/μL (range, 10-127) and the median of $CD34^+$ cells harvested was $5.2x10^6$/kg (range, 2.2-12.2), with 28/32 (88%) of patients yielding more than $4×10^6$/kg. The median number of aphereses was two (range, 1-4).

The chemo-free mobilization failed in ten patients (10%) who were subsequently given a chemo-based mobilization regimen: six patients were given cyclophosphamide and four were given high-dose cytarabine. Two patients received plerixafor on demand. One patient failed to mobilize $CD34^+$ cells. The median peak $CD34^+$ cell count was 88/μL (range, 6-624) and the median of $CD34^+$ cells harvested was $7x10^6$/kg (range, 3-15), with seven of nine (78%) patients yielding more than $4×10^6$/kg. The median number of aphereses was two (range, 1-2).

In the univariate analysis, higher Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), International Staging System (ISS) score ≥2 and a time interval from the last daratumumab administration ≥30 days had a negative impact on the number of $CD34^+$ cells harvested, while mobilization after four courses of induction was associated with more aphereses. The results are summarized in Table 2.

All parameters were evaluated both in the whole population (N=100) and in patients whose stem cells were mobilized with G-CSF alone (65/100). No factors showed a statistically significant impact in the latter group.

All patients received high-dose melphalan; the transplant

Table 1. Patients' characteristics.

Variable	Value
Age in years, median (range)	60.5 (42-71)
Female sex, N (%)	44 (44)
Male sex, N (%)	56 (56)
Ig isotype, N (%)	
IgG	66 (66)
IgA	11 (11)
Light chain only	12 (12)
Non secretory	1 (1)
Unknown	10 (10)
ISS stage, N (%)	
I	30 (30)
II	16 (16)
III	29 (29)
Unknown	25 (25)
Induction cycles, median (range)	4 (3-6)
Disease status prior to ASCT, N (%)	
Complete response	16 (16)
Very good partial response	60 (60)
Partial response	16 (16)
Stable disease	1 (1)
Unknown	7 (7)
Time from last daratumumab dose to G-CSF in days, median (range)	25 (9-109)
HCT-CI, N (%)	
0-1	59 (59)
2-4	30 (30)
>4	5 (5)
Unknown	6 (6)

ISS: International Staging System; ASCT: autologous stem cell transplant; G-CSF: granulocyte colony-stimulating factor; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index.

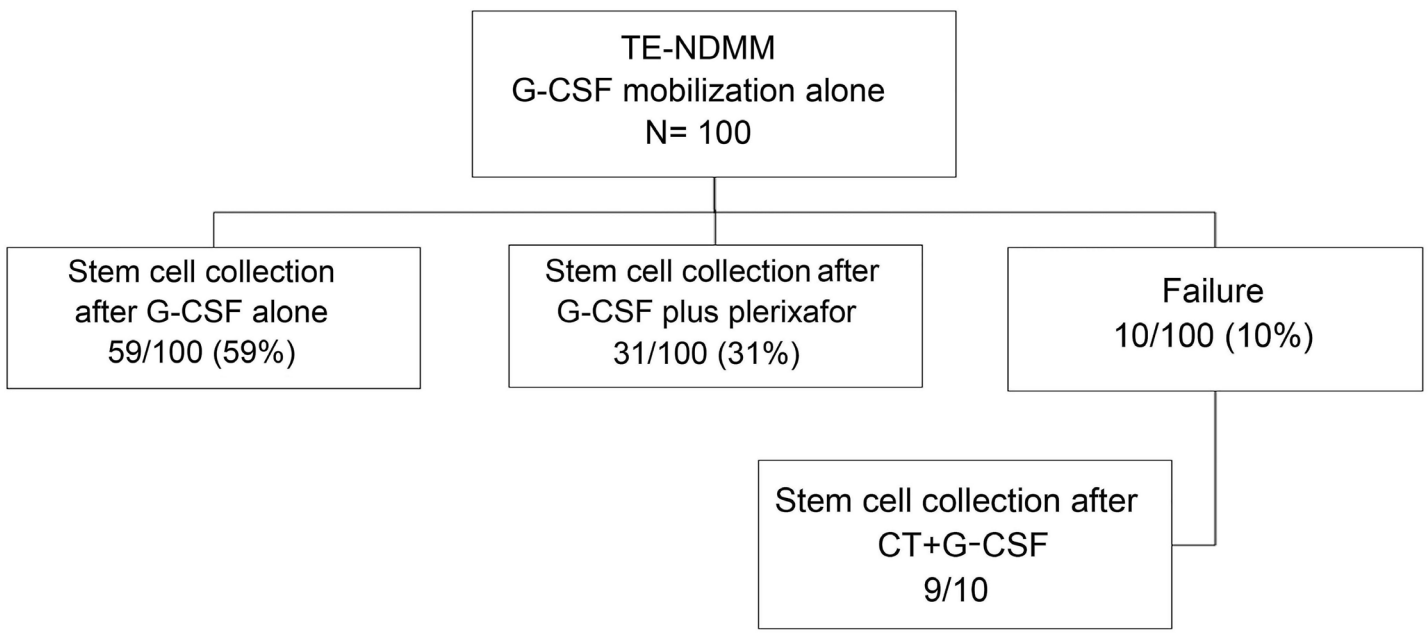

Figure 1. Flow diagram of mobilization of peripheral blood stem cells in patients with newly diagnosed multiple myeloma. TE-NDMM: transplant-eligible newly diagnosed multiple myeloma; G-CSF: granulocyte colony-stimulating factor; CT: chemotherapy.

Table 2. Univariate analysis of factors predicting mobilization endpoints.

Factors	N of CD34⁺ cells harvested		N of aphereses		Plerixafor on demand		Failure to mobilize	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age: ≥60 *vs.* <60 years	2.1 (0.5-8.7)	0.1	2.1 (0.9-5)	0.08	1.1 (0.4-2.5)	0.8	2.1 (0.5-8.7)	0.2
Gender: male *vs.* female	1.4 (0.4-4)	0.5	0.7 (0.3-1.8)	0.5	0.97 (0.4-2.2)	0.9	1.9 (0.5-8)	0.3
Disease response after induction: ≥VGPR *vs.* <VGPR	2.35 (0.4-11.4)	0.2	1.2 (0.4-3.6)	0.7	2 (0.6-6.7)	0.26	2.2 (0.3-19.2)	0.9
HCT-CI: 0-2 *vs.* >2	5.8 (1.8-18.8)	0.002	2.1 (0.8-5.1)	0.1	0.5 (0.2-1.3)	0.1	1 (0.2-4.5)	0.9
ISS score: 1 *vs.* ≥2	6.25 (1-37.6)	0.004	1.87 (0.5-4)	0.3	1 (0.3-3)	0.9	0.6 (0.1-4.3)	0.6
Isotype: IgG *vs.* other	0.9 (0.3-2.9)	0.8	1.2 (0.4-3.4)	0.6	1.1 (0.4-3)	0.7	3.4 (0.4-29)	0.2
Δ Daratumumab to G-CSF								
>25 days *vs.* <25 days	0.61 (0.2-1.7)	0.3	1.3 (0.5-3)	0.5	1.3 (0.3-3)	0.4	3.7 (0.7-19)	0.1
>30 days *vs.* <30 days	0.09 (1.2-80)	0.02	0.8 (0.3-2.2)	0.8	1 (0.4-2.3)	0.9	2.8 (0.08-1.4)	0.1
>35 days *vs.* <35 days	0.1 (0.7-50)	0.08	1 (0.4-3)	0.9	0.9 (0.4-2.7)	0.9	0.9 (0.2-5.2)	0.9
Mobilization: after 4th *vs.* 3rd cycle	0.4 (0.13-1.14)	0.08	0.4 (0.17-1)	0.05	1.06 (0.4-2.4)	0.8	1.4 (0.3-5.8)	0.6

OR: odds ratio; 95% CI: 95% confidence interval; VGPR: very good partial response; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; ISS: International Staging System; Δ Daratumumab to G-CSF: time interval from the last dose of daratumumab to administration of granulocyte colony-stimulating factor.

characteristics are listed in *Online Supplementary Table S1*. Most of the patients received melphalan 200 mg/m^2. The post-transplant course was regular, and the median time to achieve safe absolute neutrophil and platelet counts was 11 days (range, 6-24) and 14 days (range, 7-35), respectively. Daratumumab can negatively affect stem cell collection regardless of mobilization strategy.[4-13] In the phase III CASSIOPEIA study,[5] comparing bortezomib, thalidomide and dexamethasone with or without daratumumab as induction therapy, all patients were mobilized using a chemo-based strategy (cyclophosphamide 2-3 g/m^2 plus G-CSF 10 μg/kg/day): in the daratumumab-treated arm, stem cell harvest was successful in 99.6% of patients and the median number of CD34⁺ cells was 6.7x10^6/kg. Plerixafor was used in 22% of patients and the mean number of apheresis sessions was 1.9. In the phase II GRIFFIN[6] and MASTER[7] studies daratumumab was combined with lenalidomide, a drug already having a well-known negative impact on stem cell mobilization. In both studies a chemo-free mobilization strategy was adopted and plerixafor was used randomly upfront or as a rescue strategy after the failure of G-CSF. The *post-hoc* analysis of these two studies conducted by Chhabra *et al.*[5] showed that: (i) the median stem cell yield was 8.3×10^6 CD34⁺ cells/kg in the GRIFFIN study and 6×10^6 CD34⁺ cells/kg in the MASTER study; (ii) plerixafor was used in 89% and 41% of cases, respectively; and (iii) the mobilization failure rate was 2% and 7%, respectively.[15]

Overall, data from more recent "real-life" studies[8-13] on stem cell mobilization in TE-NDMM patients treated with a daratumumab-based induction reproduce those from these prospective trials. In only one study, by Thurlapaty *et al.*,[10] was a chemo-free strategy used. As far as we know, our study represents the largest analysis of chemo-free mobilization in a real-life setting. A comparison of our data with those of the main "real-life" studies is reported in *Online Supplementary Table S2*. As a result of the univariate analysis of our study (Table 2), some interesting new findings emerged. First, patients undergoing four cycles of induction experienced more aphereses (>1 days) than patients undergoing three cycles. Moreover, the probability of achieving a higher number of CD34⁺ cells was higher when the HCT-CI was <2 and ISS score <2. In contrast, a greater delay between last daratumumab dose and G-CSF (>30 days) significantly improved the amount of CD34⁺ cells harvested.

Even though our study is a retrospective analysis with inherent selection bias, its strength lies in the homogeneous patient population treated with the same induction therapy and mobilization protocol (G-CSF and plerixafor on demand). Overall, our results show that in the era of daratumumab-based quadruplet therapy, chemo-free mobilization is feasible, safe, and effective for harvesting a sufficient number of CD34⁺ cells to complete the induction program with one or two courses of high-dose melphalan. A longer wash-out from daratumumab (>30 days) seems to be associated with a better CD34⁺ cell harvest. However, it should be pointed out that chemo-based mobilization is more efficient and should, therefore be preferred when tandem high-dose chemotherapy is planned.

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Contributions

All authors contributed to patients' clinical care and collecting data. MP and LC wrote the manuscript. CCo analyzed the data. LC contributed to the design of the study and critically reviewed the data and manuscript. All authors read and agreed to the published version of the manuscript.

Data-sharing statement

Original data are available in anonymous form upon request by contacting the corresponding author.

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