haematologica
Journal of the Ferrata Storti Foundation

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Received: July 24, 2024.
Accepted: October 22, 2024.

Citation: Marika Porrazzo, Tiziana Moscato, Giuseppe Sapienza, Fabrizio Accardi, Caterina Patti, Clotilde Cangialosi, Carmelo Costanza, Roberto Bono, Stefania Tringali, Cristina Rotolo, Emilia Gigliotta, Andrea Rizzuto, Manuela Giuseppa Ingrascì, Giulia Butera, Laura Di Noto, Alessandra Santoro, Anna Marfia, Cirino Botta, Sergio Siragusa, Massimo Martino, and Luca Castagna.- Impact of daratumumab/bortezomib/thalidomide and dexamethasone induction therapy on chemo-free stem cell mobilization in transplant eligible newly diagnosed multiple myeloma: a multicentre real-world experience.
Haematologica. 2024 Oct 31. doi: 10.3324/haematol.2024.286332 [Epub ahead of print]

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

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Disclosures: No conflicts of interest to disclose.

Authors' contributions: All authors contributed to patients' clinical care and collecting data. MP and LC wrote the manuscript. CC performed data analysis. LC contributed to the design of the study and critically reviewed the data and manuscript. All authors have read and agreed to the published version of the manuscript.

Data-sharing statement: original data are available in anonymous form upon request by contacting corresponding author.

Clinical Trial details. Retrospective multicentre study. This study was approved by Comitato Etico Territoriale Sicilia (Italy), EudraCT number 1199, 17/4/2024.

Transplant-eligible newly diagnosed multiple myeloma (TE-NDMM) patients are currently treated with quadruplet induction therapy including anti-CD38 monoclonal antibody (mAb) Daratumumab (dara) followed by 1 or 2 high-dose melphalan (HD-PAM) and autologous stem cell transplantation (ASCT)[1]. The mobilization of peripheral blood stem cells (PBSC) is crucial to successfully carrying out the transplant program and it can be accomplished using a conventional chemotherapy, most frequently cyclophosphamide (2-4 g/m2) combined with granulocyte colony stimulating factor (G-CSF), or a chemo-free therapy with G-CSF alone, plus/minus plerixafor[2,3].

Recently, with the wide use of anti-CD38 mAb (daratumumab, isatuximab) during the induction phase a growing concern about the PBSC mobilization has arisen. Although there is no clear understanding of the underlying mechanism, many authors speculate that in patients treated with anti-CD38+ mAb leukocytes, stromal cells, or endothelial cells overexpress adhesive molecules negatively affecting mobilization[4].

Regardless the mobilization strategy adopted, data from the largest randomized clinical trials comparing Dara-based regimens showed a higher use of plerixafor, more leukaphereses and lower stem cell yields in patients receiving dara. However, in all trials, most patients received the planned ASCT [5,6,7].

The impact of Dara on stem cell mobilization has recently been reported in retrospective real-life studies [8-13].

In this large observational retrospective study, we analyzed TE-NDMM treated with quadruplet Dara-VTD and mobilized with a chemo-free strategy (G-CSF and plerixafor on demand) at two Italian centers. Our goal was to assess the success of the mobilization particularly with regard to the mobilization failure rate, CD34+ harvested and the need for plerixafor administration.

From January 2022 to January 2024, 100 TE-NDMM were included. The diagnosis and response criteria was defined according to the International Myeloma Working Group (IMWG) criteria[14].

The target stem cell mobilization was $2.0x10^6$ cells/kg for 1 ASCT and $4x10^6$ cells/kg for 2 ASCT. According to our institutional mobilization protocol, patients received subcutaneous G-CSF 10 mcg/day from day +1. CD34+ cell count was started at day +5 and leukapheresis was started as well in case they were more than 20 µl/L and continued for 1 to 4 days until the target achievement. Plerixafor 240 mcg/kg was administered *on demand* 6-11 hours before apheresis, if circulating CD34+ were less than 20 µl/L at day +5. A CD34+ yield $<2.0\times10^6$/kg was considered as failure. Patients who failed chemo-free mobilization underwent to a second chemo-based strategy to harvest stem cells. The chemotherapy consisted of cyclophosphamide (2 g/m^2) and high-dose cytarabine (1600 mg/m^2) plus G-CSF 5 mcg/day from days +6. Conditioning regimen consisted of high dose of melphalan (200 mg/m^2 or 140 mg/m^2 in case of renal impairment or age ≥65 years). Stem cells were infused the day after (d 0) through central vein access.

For data collection the approval of the local Ethics Committee was obtained, and all patients provided a written informed consent.

The statistical analysis was performed using R- studio version 4.1.2; categorical variables were reported as count with percentage and continuous variables as median with range. Chi-square 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+ (<4 vs ≥4) was performed. The final logistic regression model was used to estimate odds ratios (ORs), 95% confidence intervals (CIs), and p value.

Patient baseline characteristics were reported in the **Table 1**. 100 patients with a median age of 61 years (range 42-71) were included. Median induction cycles were 4 (3-6). Responses to induction were: CR 16%, VGPR 60%, PR 16%, SD 1% and unknown in 7%. Patients flow was reported in the **Figure 1**.

63% of patients were mobilized after 4 cycles and 37% after 3 cycles. The median time from last Dara infusion to G-CSF start was 25 days (range 9-109). Overall, PBSC harvest after the first chemo-free mobilization was successful in 90% of patients: in 58/90 (64%) optimal stem cell harvest was obtained after GSCF alone, while plerixafor *on demand* was added in 31/90 patients (36%). 77/90 (86% of patients) harvested more than $4x10^6$/kg CD34+ cells.

In the cohort mobilized with GCSF alone (n= 58), the median CD34+ peak was 58/µL (range 16-490) and the median of CD34+ cells harvested was $6.2x10^6$/kg (1.3-23.9), with 49/58 (84%) patients harvesting more than $4×10^6$/kg. The median number of apheresis was 2 (range 1-3).

In the cohort mobilized adding plerixafor *on demand* (n= 31), the median CD34+ peak was 48.5/µL (10-127) and the median of CD34+ cells harvested was $5.2x10^6$/kg (2.2-12.2), with 28/32 (88%) of patients harvesting more than $4×10^6$/kg. The median number of apheresis was 2 (range 1-4).

The chemo-free mobilization failed in 10 patients (10%) and they were mobilized with chemo-based regimen. 6 patients were mobilized using Cy and 4 using high-dose cytarabine. 2 patients received plerixafor *on demand*. One patient failed to mobilize CD34+ cells. The median CD34+ peak was 88/µL (range 6-624) and the median of CD34+ cells harvested was $7x10^6$/kg (3-15), with 7/9 (78%) patients harvesting more than $4×10^6$/kg. The median number of apheresis was 2 (range 1-2).

In the univariate and analysis, higher comorbidity index, International Staging System (ISS) ≥ 2 and a time interval from the last dara administration ≥30 day (Δ dara) had a negative impact on the number of CD34+ cells harvested, while mobilization after the 4 courses of induction was associated to more aphereses. Results are summarized in **Table 2**.

All these parameters were evaluated both in the whole population (n=100) and in patients mobilizing with G-CSF alone (65/100). No factors showed statistically significant impact in the latter group.

All patients received HD-PAM; the transplant characteristics are depicted in **Supplementary Table 1.** Most of the patients received HD-PAM 200 mg/m^2. The post-transplant was regular, and the median time to achieve a safe absolute neutrophil count and platelet count was 11 days (range 6-24) and 14 (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 DARA-VTD vs VTD as induction therapy, all patients were mobilized using a chemo-based strategy (cyclophosphamide 2-3 g/m^2 plus G-CSF 10mcg/Kg/day) and in dara-treated arm, stem cells harvest was successful in 99.6% of patients and the median number CD34 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 dara 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 as upfront or rescue strategy after G-CSF failure. The post-hoc analysis of these 2 studies conducted by Chhabra et al.[15] showed: the median stem cells yield was 8.3×10^6 CD34+ cells/kg in the GRIFFIN and 6×10^6 CD34+ cells/kg in the MASTER and plerixafor was used in 89% and 41% of cases; finally, the mobilization failure rate was 2% and 7% respectively[15].

Data from more recent "real life" studies[8-13] on stem cell mobilization in TE-NDMM patients treated with a dara-based induction overall reproduce those from these prospective trials. In only one study by Thurlapaty et al[10] a chemo-free strategy was used. As far as we know, our study represents the largest analysis on chemo- free mobilization in a real life setting. A comparison of our data with those of the main "real-life" studies are reported in **Supplementary Table 2.** As a result of the univariate analysis of our study (**Table 2**), the following new interesting findings emerged: patients undergoing 4 cycles of induction experienced more aphereses (>1 days) than patients undergoing 3 cycles. Moreover, the probability to achieve a higher number of CD34+cells was higher when HCT-CI was <2 and ISS <2. In contrast, a great delay between last daratumumab and G-CSF (>30 days) significantly improved the amount of CD34+ 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 showed that in the era of dara-based quadruplets, chemo-free mobilization is feasible, safe, and effective to harvest a sufficient number of CD34+ cells to complete the induction program with 1 or 2 courses of HD-PAM. A longer wash-out from dara (>30 days) seems to be associated with a better CD34+ harvest. However, it should be pointed out the higher efficiency of chemo-based mobilization which thus it should be preferred when tandem HDC is planned.

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	100 (%)
Age, yr, 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 (%)	
CR	16 (16)
VGPR	60 (60)
PR	16 (16)
SD	1 (1)
Unknown	7 (7)
Time from last daratumumab to G-CSF, median days (range)	25 (9-109)
HCT-CI N (%)	
0-1	59 (59)
2-4	30 (30)
>4	5 (5)
Unknown	6 (6)

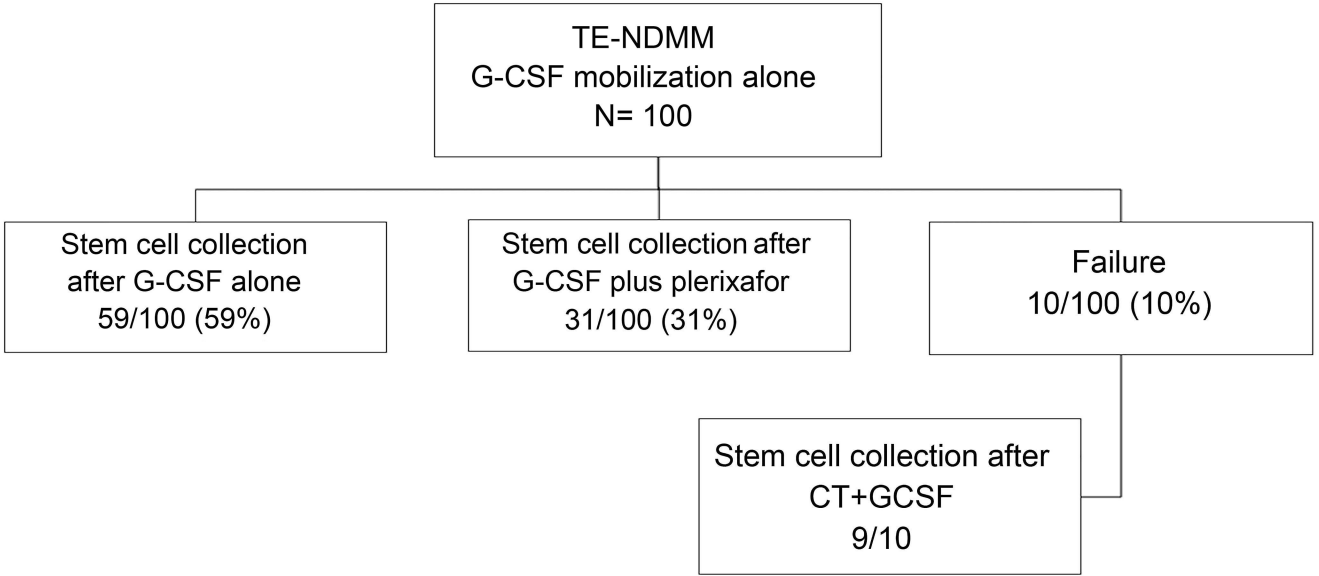
Table 1. Patient characteristics

ASCT: autologous stem cell transplant; CR: complete response; G-CSF: granulocyte colony stimulating factor; HCT-CI: Hematopoietic Cell Transplantation-specific comorbidity index; ISS: International Staging System; PR: partial response; SD: stable disease; VGPR: very good partial response.

	N CD34+ harvested		N apheresis		Plerixafor on demand		Failure to mobilize	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age ≥60y vs <60y	2.1 (0.5-8.7)	.1	2.1 (0.9-5)	**.08**	1.1 (0.4-2.5)	.8	2.1 (0.5-8.7)	.2
Gender M vs F	1.4 (0.4-4)	.5	0.7 (0.3-1.8)	.5	0.97 (0.4-2.2)	.9	1.9 (0.5-8)	.3
Disease response after induction ≥VGPR vs < VGPR	2.35 (0.4-11.4)	.2	1.2 (0.4-3.6)	.7	2 (0.6-6.7)	.26	2.2 (0.3-19.2)	.9
HCT-CI 0-2 vs >2	5.8 (1.8-18.8)	**.002**	2.1 (0.8-5.1)	.1	0.5 (0.2-1.3)	.1	1 (0.2-4.5)	.9
ISS 1 vs ≥2	6.25 (1-37.6)	**.004**	1.87 (0.5-4)	.3	1 (0.3-3)	.9	0.6 (0.1-4.3)	.6
Isotype IgG vs other	0.9 (0.3-2.9)	.8	1.2 (0.4-3.4)	.6	1.1 (0.4-3)	.7	3.4 (0.4-29)	.2
Δ Dara-G-CSF >25 days vs <25 days	0.61 (0.2-1.7)	.3	1.3 (0.5-3)	.5	1.3 (0.3-3)	.4	3.7 (0.7-19)	.1
Δ Dara-G-CSF >30 days vs <30 days	0.09 (1.2-80)	**.02**	.8 (0.3-2.2)	.8	1 (0.4-2.3\)	.9	2.8 (0.08-1.4)	.1
Δ Dara-G-CSF >35 days vs <35 days	0.1 (0.7-50)	.08	1 (0.4-3)	.9	.9 (0.4-2.7)	.9	.9 (0.2-5.2)	.9
Mobilization after 4^{th} vs 3^{th} cycle	0.4 (0.13-1.14)	.08	0.4 (0.17-1)	**.05**	1.06 (0.4-2.4)	.8	1.4 (0.3-5.8)	.6

Table 2. Univariate analysis of factors predicting mobilization end points. CI: confidence interval; Dara: daratumumab; HCT-CI: Hematopoietic Cell Transplantation-specific comorbidity index; ISS: international staging system; OR: odds ratio; VGPR: very good partial response.

Figure 1. Mobilization patients flow.


TE-NDMM
G-CSF mobilization alone
N= 100
Stem cell collection
after G-CSF alone
59/100 (59%)
Stem cell collection after
G-CSF plus plerixafor
31/100 (31%)
Failure
10/100 (10%)
Stem cell collection after
CT+GCSF
9/10

	N= 99
Age, yr, median (range)	60,5 (42-71)
PAM dose 140 mg/m^2 200 mg/m^2	 34 66
Median number CD34+ infused (x10^6/kg)	4 (2-7.8)
Median time to ANC > 0.5 (x10^9/L)	11 days (6-24)
Median time to PLT > 20 (x10^9/L)	14 days (7-35)

Supplementary Table 1. Transplant characteristics.

ANC: absolute neutrophil count; PAM: melphalan; PLT: platelets

	N Dara	Induction	Mobilization strategy	Mobilization scheme	Plerixafor	CD34 collection target	CD34 trigger	CD34 peak	CD34 yield LK1	N CD34+ overall	Pts harvesting >4x106/kg	Plerixafor use	Mobilization failure
Thurlapati A et al. [10]	43	Dara-VRD	Chemo-free	G-CSF + Plerixafor	Pre-emptive	≥2.5x10^6/kg ≥5x10^6/kg	NR	43 µL	4.9x10^6/kg	6.54 x10^6/kg	/	§51%	No
Papaiakovou E et al. [14]	40	Dara-VRD/VCD/VTD/KRD	Chemo-based	Cy 2.5 g/m^2 + G-CSF	On demand	/	/	/	/	10.4 x10^6/kg	/	42%	/
Sauer S et al. [11]	68	Dara-VTD	Chemo-based	CAD or Cy + G-CSF	On demand	≥6x10^6/kg	10 µL	65 µL	5.5x10^6/kg	8.4 x10^6/kg	/	33%	No
Mina R et al. [15]	10	Dara-VTD	Chemo-based	Cy 2-4 g/m2 + G-CSF	On demand	≥2x106/kg	20 µL	60 µL	9.9x10^6/kg	9.9x10^6/kg	95%	13%	4%
Zappaterra A et al[12]	20	Dara-VTD	Chemo-based	Cy 2-3 g/m^2 + G-CSF	On demand	≥6x10^6/kg	20 µL	38 µL	3.9x10^6/kg	3.9 x10^6/kg	/	20%	NR
Liberatore C et al. [13]	47	Dara-VTD	Chemo-based	Cy 4 g/m^2	On demand	≥6x10^6/kg	NR	NR	6.9x10^6/kg	10.6 x10^6/kg	/	49%	7%
This study	100	Dara-VTD	Chemo-free	G-CSF	On demand	≥6x10^6/kg	20 µL	58 µL	6.2x10^6/kg	6.2x10^6/kg	86%	36%	10%

Supplementary Table 2. PBSC mobilization/collection parameters reported in “real life” studies compared with our study.

§ in this study, plerixafor was used in front-line and 51% means that patients needed of 2nd administration.

CAD: cyclophosphamide, adriamycin, dexamethasone; Cy: cyclophosphamide; Dara-VRD: daratumumab, bortezomib, lenalidomide, dexamethasone; Dara-VTD: daratumumab, bortezomib, thalidomide, dexamethasone; G-CSF: granulocyte colony stimulating factor; KRD: carfilzomib, lenalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; VTD: bortezomib, thalidomide, dexamethasone.