The impact of daratumumab-containing induction on stem cell mobilization, collection and engraftment in newly diagnosed multiple myeloma: results of the prospective DILEMMA study

Autologous stem cell transplantation (ASCT) is still considered the gold standard of intensification therapy for younger fit patients with newly diagnosed multiple myeloma (NDMM).[1] For this purpose, apheresis procedures should secure a minimum cell dose of $2x10^6$ $CD34^+$ cells/kg for a single transplant, with the goal of collecting at least $4x10^6$ $CD34^+$ cells/kg for patients presenting cytogenetic high-risk status to support a second ASCT.[2] The incorporation of anti-CD38 monoclonal antibodies (mAb) into induction regimens has led to deeper clinical responses, but concerns have emerged regarding the potential negative effects on stem cell mobilization and collection, even if causative mechanisms have not so far been identified.[3,4] In clinical trials, decreased yield of mobilized $CD34^+$ cells in apheresis products, prolonged days of collection, and increased use of plerixafor are, in fact, reported in patients receiving daratumumab-induction regimens.[5-7]

DILEMMA (Daratumumab-containing Induction effects on stem cells mobilization, colLection, and Engraftment in newly diagnosed Multiple MyelomA patients) is a single-center study prospectively investigating daratumumab effects on stem cell mobilization and collection in NDMM patients. The study was carried out at Fondazione Policlinico "A. Gemelli" IRCCS from February 2023 to December 2024. NDMM patients treated with daratumumab-containing induction regimens and candidates for ASCT were enrolled at the time of stem cell mobilization. As control group, NDMM patients treated at the same hospital from 2019 to 2021 (before the introduction of daratumumab) were retrospectively enrolled. The study was approved by the institutional Ethic Committee (protocol n. 0003280/23) and registered at *clinicaltrials.gov NCT05835726*. Signed informed consent was obtained from all patients. The primary outcome was the completion at first apheresis of a target cell dose $\geq 4x10^6$ $CD34^+$ cells/kg patient body weight (EBMT guidelines for tandem ASCT).[2] Secondary outcomes were the median dose of $CD34^+$ cells/kg at first apheresis (normalized to 10 L of blood volume processed),[8] the proportion of patients needing plerixafor, the rate of mobilization failures, engraftment time, and transfusion requirements after ASCT. Group comparison was carried out in the entire population, and after matching daratumumab-treated patients and controls for baseline characteristics which significantly differed at univariate analysis ($P \leq 0.05$). For this purpose, a Propensity Score Match (PSM) was computed using a logistic regression model with daratumumab *versus* no-daratumumab as dependent variable, and greedy matching algorithms without replacement for the identified variables. The mobilization regimen consisted of 2-4 g/m^2 cyclophosphamide followed by 5 μg/kg/die granulocyte-colony stimulating factor (G-CSF) from day +3 after completion of chemotherapy. Plerixafor was administered on demand at the dose of 240 μg/kg/day 6-8 hours (hr) before leukapheresis, if the expected peak of $CD34^+$ cell count was <20 cells/μL or estimated collection harvest $<1x10^6$/kg. If less than $2x10^6$ $CD34^+$ cells/kg were collected, additional plerixafor administration and further apheresis were performed. Mobilization failure was defined as not being able to collect $\geq 2x10^6$ $CD34^+$ cells/kg body weight.

Overall, 66 daratumumab-treated patients were compared with 84 retrospective controls (*Online Supplementary Figure S1*). *Online Supplementary Table S1* summarizes clinical and laboratory characteristics and ASCT outcomes of the investigated population. The two groups were comparable for demographic and disease-related variables, whereas the cyclophosphamide dose at mobilization was significantly lower in the daratumumab group (median dose 2.9 g/m^2 and 3.9 g/m^2 in daratumumab patients and controls, respectively; $P<0.001$). After matching by cyclophosphamide dose, 44 patients per group were identified (*Online Supplementary Figure S1*). Patient characteristics and mobilization outcomes of the two groups are reported in Table 1 and illustrated in Figure 1. No differences emerged between matched groups regarding the proportion of patients achieving $\geq 4x10^6$ $CD34^+$ cells/kg at first apheresis. Nonetheless, compared to controls, daratumumab-patients had a lower peripheral blood (PB) $CD34^+$ cell concentration on the day before apheresis (22/μL and 36/μL median values in patients and controls, respectively; $P=0.021$) and at first apheresis (58/μL and 98.5/μL median values in patients and controls, respectively; $P=0.034$). Accordingly, the daratumumab-patients experienced an inferior $CD34^+$ yield at first apheresis (3.8 and 6.3×10^6/kg, in patients and controls, respectively; $P=0.029$). Overall, no patients failed to collect at least $2x10^6$ $CD34^+$ cells/kg, despite more daratumumab-patients needed plerixafor (27.3% and 9.1% in patients and controls, respectively; $P=0.027$). Finally, no differences emerged between matched groups regarding the number of leukapheresis. Overall, 41 out of 44 patients (93.2%) performed one ASCT, while 19 (43.2%) underwent

Table 1. Baseline clinical and laboratory characteristics and outcome data of 88 Propensity Score Matched patients grouped according to daratumumab administration.

Patient characteristics	Daratumumab N=44	Controls N=44	*P*
Basal demographics			
Age at diagnosis, years, median (IQR)	59 (54-65)	61 (57-66)	0.249
Males, N (%)	15 (34.1)	18 (40.9)	0.509
Body weight, kg, median (IQR)	73 (65-85)	75 (66-87)	0.707
Ig isotype, N (%)			
IgG	25 (56.8)	22 (50.0)	0.729
IgA°	9 (20.4)	10 (22.7)	
IgM	1 (2.3)	0	
Light chains	8 (18.2)	10 (22.7)	
Others§	1 (2.3)	2 (4.6)	
Laboratory parameters at diagnosis			
Hemoglobin, g/dL, median (IQR)	12.2 (10.4-13.1)	11.0 (9.6-13.6)	0.310
Creatinine, mg/dL, median (IQR)	0.91 (0.78-1.27)	0.95 (0.75-1.30)	0.882
Calcium, mg/dL, median (IQR)	9.6 (9.1-10.0)	9.7 (9.4-10.3)	0.174
LDH, mU/mL median (IQR)	158 (142-204)	164 (136-194)	0.762
Albumin, g/dL, median (IQR)	3.8 (3.2-4.2)	3.9 (3.4-4.4)	0.441
Positive Bence Jones protein, N (%)	23 (52.3)	19 (43.2)	0.480
High cytogenetic risk, N (%)*	11 (28.9)	8 (22.2)	0.508
ISS score, N (%)			
1	22 (50.0)	22 (50.0)	0.745
2	10 (22.7)	13 (29.5)	
3	12 (27.3)	9 (20.5)	
R-ISS score, N (%)*			
1	11 (28.9)	14 (40.0)	0.655
2	23 (60.5)	17 (48.6)	
3	4 (10.5)	4 (11.4)	
Bone lesion, N (%)	33 (75.0)	34 (77.3)	0.802
Therapy, N (%)			
Lenalidomide	-	1 (4.6)	0.153
Radiotherapy	3 (6.8)	-	0.078
Disease status at mobilization, N (%)			
sCR/CR	11 (25.0)	12 (27.3)	0.832
VGPR	16 (36.4)	12 (27.3)	
PR	17 (38.6)	20 (45.4)	
Cyclophosphamide dose, g/m^2, median (IQR)	3.3 (2.8-3.9)	3.3 (2.9-3.9)	0.920
Cyclophosphamide ≥3 gr/m^2, N (%)	35 (81.1)	36 (79.6)	0.787
Total BVP, L, median (IQR)	15.1 (13.0-16.3)	14.1 (11.8-16.2)	0.084
Outcomes			
Day -1 CD34$^+$ cells/μL, median (IQR)	22.0 (11.0-41.0)	36.0 (19.5-76.5)	0.021**
Day 0 CD34$^+$ cells/μL, median (IQR)	58.0 (40.0-146.0)	98.5 (57.5-144.8)	0.034**
CD34$^+$ cells ≥4x10^6/kg at first apheresis, N (%)	33 (75.0)	37 (84.1)	0.290
CD34$^+$ cells x10^6/kg/10 L BVP at first apheresis, median (IQR)	3.8 (2.6-9.3)	6.3 (4.3-9.3)	0.029**
CD34$^+$ cell x10^6/kg at first apheresis, median (IQR)	5.8 (4.0-12.0)	8.8 (6.1-13.4)	0.081
Plerixafor, N (%)	12 (27.3)	4 (9.1)	0.027**
Days of collection, N (%)			
1	17 (38.6)	23 (52.3)	0.101
2	26 (59.1)	17 (38.6)	
3	1 (2.3)	4 (9.1)	

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°One patient exhibited double monoclonal component IgA and IgG. §This group included 2 patients with plasmacytoma and one patient with non-secretory multiple myeloma. *At diagnosis, cytogenetic and subsequently Revised International Staging System (R-ISS) were evaluated in 73 cases: 38 in the daratumumab patients and 35 in the controls. Day 0 is defined as the first day of apheresis. BVP: blood volume processed; CR: complete response; CTX: cyclophosphamide; IQR; Interquartile Range; LDH: lactate dehydrogenase; N: number; PR: partial response; sCR; stringent CR; VGPR: very good partial response. **Statistically significant.

a second ASCT (Table 2). Among the controls, one ASCT was performed in 43 cases (97.7%), and 2 transplants in 37 (84.0%). The ASCT conditioning regimen consisted of a high dose of melphalan (200 mg/m^2 body surface), reduced to 140 mg/m^2 in case of renal impairment or age ≥65 years. All patients and controls received 30 μU/die G-CSF from day +6 until neutrophil engraftment.[2] Of note, the infused graft exhibited comparable CD34$^+$ cell numbers between patients and controls, both at the first and second ASCT. Hematopoietic recovery was obtained in all patients: the time for neutrophil and platelet engraftment were similar in the two groups, whereas daratumumab-receiving patients experienced higher platelet transfusion needs only at the first ASCT (*P*=0.022).

To the best of our knowledge, our study represents the first prospective investigation exploring stem cell mobilization in transplant eligible NDMM patients after daratumumab-containing induction therapy. The clinical advantage conveyed by daratumumab in this setting renders it unethical to randomize patients to receive or not receive this therapy.[5-7] For this reason, we used a PSM approach to carry out a reliable assessment of the effects of daratumumab-containing induction on stem cell mobilization. Although there were no relevant changes in the management of NDMM patients during the study period (apart from the daratumumab introduction), we observed a progressive reduction in the cyclophosphamide dosage from 2022 onward, in line with a general trend to limit toxicity in MM patients and reflecting the wider access to transplants of more fragile patients in recent years.[9] Indeed, in PSM matched groups, the proportion of patients receiving ≥3g/m^2 cyclophosphamide was very similar (81.1% among daratumumab-patients and 79.6% among controls, respectively) (Table 1), explaining the similar proportion of patients completing the target cell dose ≥4x10^6 CD34$^+$ cells/kg at first apheresis (75.0 % and 84.1% in daratumumab and control patients, respectively).

Table 2. Transplant outcomes at first and second autologous stem cell transplantation in patients receiving daratumumab and controls selected after the Propensity Score Match for the cyclophosphamide dose.

First ASCT	Daratumumab	Controls	*P*
	N=41	N=43	
Melphalan dose, N (%) 140 mg/m^2 200 mg/m^2	 3 (7.3) 38 (92.7)	 9 (20.9) 34 (79.1)	0.117
CD34$^+$ cell transplant dose, x10^6/kg, median (IQR)	3.4 (2.9-4.2)	3.2 (2.8-3.6)	0.200
Patients needing RBC transfusions, N (%)	10 (24.4)	13 (30.2)	0.628
Patients needing PLT transfusions, N (%)	32 (78.0)	23 (53.5)	0.022**
Time to ANC engraftment, days, median (IQR)	12 (11-13)	12 (11-12)	0.399
Time to PLT engraftment, days, median (IQR)	13 (12-14)	12 (12-14)	0.385
Total inpatient days after conditioning, N (%)	16 (15-16)	15 (15-17)	0.646
Second ASCT	**N=19**	**N=37**	
Melphalan dose, N (%) 140 mg/m^2 200 mg/m^2	 2 (10.5) 17 (89.5)	 8 (21.6) 29 (78.4)	0.466
CD34$^+$ cell transplant dose, x10^6/kg, median (IQR)	3.4 (3.1-4.3)	3.2 (2.8-3.7)	0.268
Patients needing RBC transfusions, N (%)	2 (10.5)	8 (21.6)	0.466
Patients needing PLT transfusions, N (%)	14 (73.7)	18 (48.6)	0.092
Time to ANC engraftment, days, median (IQR)	12 (11-12)	12 (11-12)	0.879
Time to PLT engraftment, days, median (IQR)	12 (12-13)	12 (11-13)	0.543
Total inpatient days after conditioning, N (%)	14 (14-16)	15 (14-16)	0.269

ANC: absolute neutrophil count; ASCT: autologous stem cell transplantation; IQR: Interquartile Range; N: number; PLT: platelets; RBC: red blood cells. **Statistically significant.

Nonetheless, we cannot exclude the possibility that this finding might, in part, be related to the lower number of patients included in the matched analysis. Apart from this finding, however, we could confirm the detrimental effect of daratumumab on stem cell mobilization, with a lower concentration of circulating CD34$^+$ cells in daratumumab-treated patients both on the day before and at first apheresis, leading to a lower stem cell yield and a more frequent need for plerixafor (Table 1 and Figure 1).

The impact of daratumumab-based induction on stem cell mobilization has been evaluated in several retrospective studies regardless of mobilization strategies, which currently appear heterogeneous among institutions, making it difficult to compare published reports.[3,10,11] *Online Supplementary Table S2* lists the main studies exploring the impact of daratumumab on stem cell mobilization and collections published between 2021 and 2025. It emerges that no standardized approaches are defined as the optimal mobilization strategy when anti-CD38 mAb are used. Cyclophosphamide plus G-CSF is the most common chemotherapy-mobilizing regimen, with dosages ranging from 1.5 to 4 g/m^2 (*Online Supplementary Table S2*), with an evident relation between cyclophosphamide dosage and CD34$^+$ cell mobilization.[12]

Our observations are in line with other studies reporting an increased use of plerixafor, both on-demand and as rescue, among daratumumab-treated patients (*Online Supplementary Table S2*). A recent real-world analysis evaluating the impact of anti-CD38 therapy on stem cell mobilization in 375 transplant-eligible NDMM showed a consistent association between anti-CD38 mAb exposure and reduced stem cell yield, necessitating twice the number of plerixafor doses to meet the minimum stem cell threshold for ASCT and back-up product. Interestingly, the associated cost-effectiveness analysis estimates that plerixafor added over $23,285 per patient in mobilization costs.[13] Indeed, despite its potential clinical advantages, the costs associated with plerixafor are the determining factor limiting its use. There is ongoing debate regarding the cost-effectiveness of a plerixafor up-front mobilization strategy, which some authors suggest significantly reduces the number of days of apheresis and improves collection yield without increased overall cost per patient.[14]

Data regarding the time to engraft in patients receiving daratumumab are scarce and conflicting (*Online Supplementary Table S2*). We observed no graft failure, the CD34$^+$ cell amount in infused grafts was comparable between groups, and times to neutrophil and platelet engraftment were similar. Despite this, at first ASCT, similarly to previous data, daratumumab-treated patients experienced higher platelet transfusion needs, denoting a more pronounced effect on hematopoiesis recovery.[15]

The main limitations of our study are the non-randomized design, short follow-up of most patients, and analysis of a limited set of variables that potentially influence the engraftment. At the same time, the strength lies in the ho-

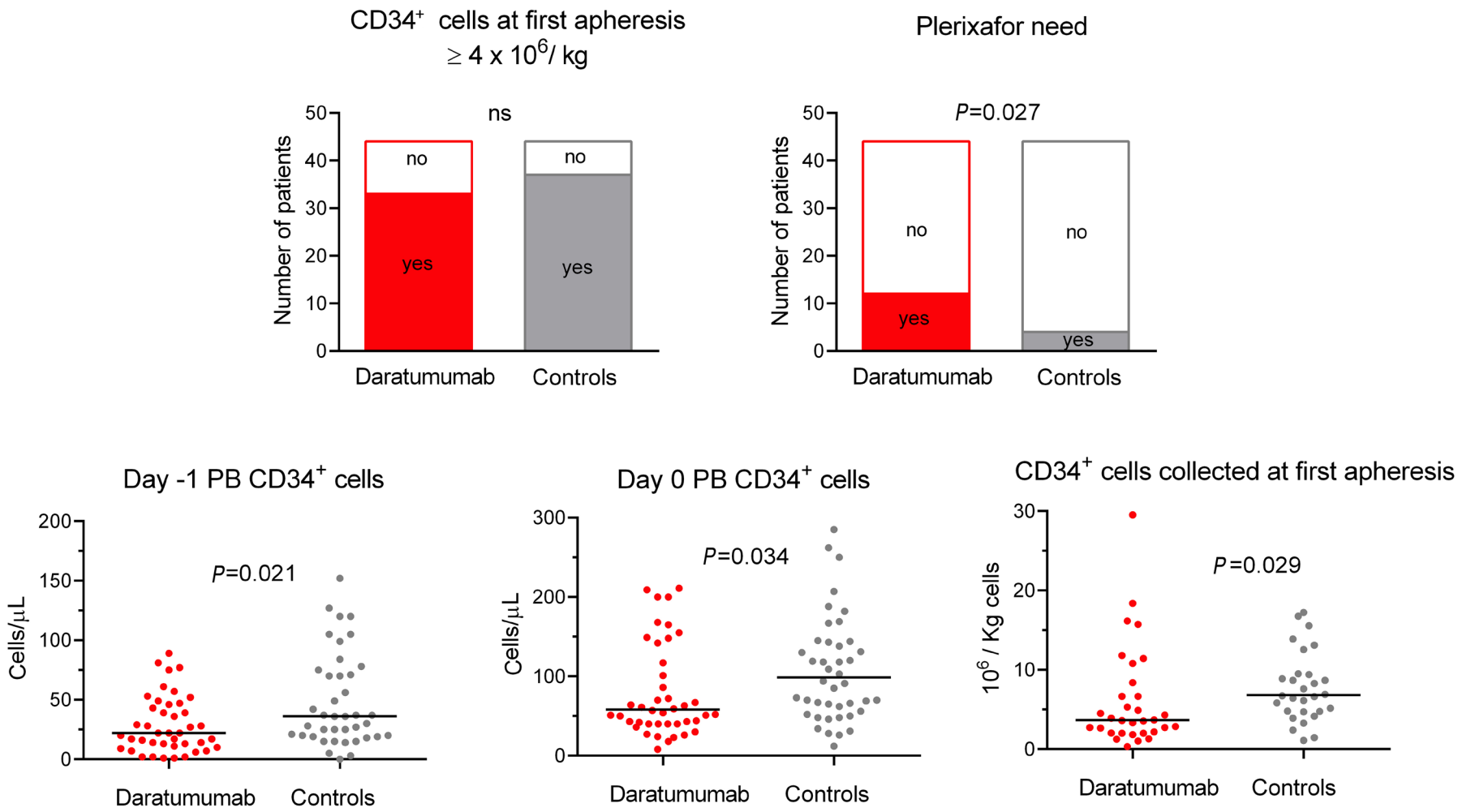

Figure 1. Study outcomes in the Propensity Score Matched patients grouped according to daratumumab administration.

mogeneity of the study population and prospective design. In conclusion, the current study is the first to prospectively explore ASCT mobilization and collection in NDMM patients receiving daratumumab induction regimens, followed by a cyclophosphamide-based mobilization strategy with G-CSF plus on-demand plerixafor, proving that the dose of cyclophosphamide has a substantial role in stem cell mobilization even in patients receiving daratumumab. Our results also show that daratumumab exposure during induction may interfere with stem cell mobilization, but this does not preclude the successful collection of adequate transplant doses of PB stem cells, even if with a higher on-demand plerixafor administration. These findings support the need for tailored mobilization strategies in patients exposed to anti-CD38 mAb. Prospective evaluations of personalized protocols are warranted to optimize efficiency and estimate the cost-effectiveness in the transplant setting, especially for high-risk selected NDMM patients, where a higher number of CD34$^+$ stem cells for tandem ASCT should still be considered, with a non-negligible impact on financial resources.

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Disclosures

No conflicts of interest to disclose.

Contributions

CGV, CP, and LT are responsible for study conception and design, data acquisition, analysis and interpretation, wrote the article, and gave final approval of the submitted version; RL and TZ are responsible for data acquisition, analysis and interpretation, and gave final approval of the submitted version; PC, LP, ER, SS and VDS critically reviewed the work for important intellectual content, wrote the article, and gave final approval of the submitted version.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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