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Autologous Stem Cell Collection after Daratumumab, Bortezomib, Thalidomide, and Dexamethasone versus Bortezomib, Cyclophosphamide, and Dexamethasone in Newly Diagnosed Multiple Myeloma

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Keywords
Multiple myeloma · Stem cell collection · Leukapheresis · Daratumumab · Thalidomide

Abstract

Introduction: In transplant-eligible, newly diagnosed multiple myeloma (NDMM) patients, autologous peripheral blood stem cell (PBSC) collection is usually pursued after induction therapy. While induction regimens are constantly refined regarding response, their impact on PBSC collection is not fully studied. The inclusion of the anti-CD38 antibody daratumumab into induction therapy significantly improved outcomes for patients with NDMM, e.g., as part of the daratumumab, bortezomib, thalidomide, and dexamethasone (Dara-VTD) protocol. Preliminary data from the phase 3 CASSIOPEIA study proved the efficacy of Dara-VTD. While overall PBSC collection upon addition of daratumumab was reduced in the study population, more detailed analyses on the impact are missing. ***Methods:*** We here report on PBSC mobilization and collection metrics in $n = 119$ patients with NDMM who underwent induction therapy with bortezomib, cyclophosphamide, and dexamethasone (VCD, $n = 61$) or Dara-VTD ($n = 58$). ***Results:*** Patient characteristics were well balanced between groups. The Dara-VTD group showed improved response parameters with 66% of patients reaching at least very good partial response versus 54% in the VCD group. Dara-VTD patients exhibited inferior mobilization metrics such as peripheral blood $CD34^+$ cell count at the first leukapheresis (LP) session (65 vs. 106/µL, $p = 0.001$), median number of LP sessions (2 vs. 1, $p = 0.001$), and PBSC collection at first LP (5.5 vs. 8.3×10^6/kg body weight [bw], $p = 0.001$). Utilization of plerixafor was slightly higher after Dara-VTD (33% vs. 21% of patients, $p = 0.143$). The overall PBSC collection result was significantly lower after Dara-VTD (8.4 vs. 9.6 $\times 10^6$/kg bw, $p = 0.026$). 78% and 85% of patients successfully collected 3 transplants with $\geq 2 \times 10^6$ $CD34^+$ cells/kg bw in the Dara-VTD and the VCD groups, respectively. ***Conclusion:*** In summary, Dara-VTD, possibly due to both anti-CD38 antibody and thalidomide exposure, imposes a limitation on PBSC collection which can be only partly overcome by utilization of plerixafor.

Introduction

In fit newly diagnosed multiple myeloma (NDMM) patients, induction followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) is standard-of-care [1–5]. In high-risk subgroups, tandem HDCT/ASCT prolongs progression-free survival [6–8]. Furthermore, HDCT/ASCT can be performed at relapse or as consolidation after salvage

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Table 1. Induction and mobilization therapy

Induction protocol	Dose	Application	Treatment days
Dara-VTD (28 days/cycle, 4 cycles)			
Daratumumab	1,800 mg	SC	Cycle 1–2: 1, 8, 15, 22 Cycle 3–4: 1, 15
Thalidomide	100 mg	PO	1–28
Bortezomib	1.3 mg/qm	SC	1, 4, 8, 11
Dexamethasone	40 mg	PO	1, 2, 8, 9, 15, 16, 22, 23
VCD (21 days/cycle, 4 cycles)			
Bortezomib	1.3 mg/qm	SC	1, 4, 8, 11
Cyclophosphamide	900 mg/qm	IV	1
Dexamethasone	20 mg	PO	1, 2, 4, 5, 8, 9, 11, 12
Mobilization protocol			
CAD			
Cyclophosphamide	1,000 mg/qm	IV	1
Doxorubicin	15 mg/qm	IV	1–4
G-CSF	5–10 µg/kg bw[1]	IV	9, 10, 11, 12, 13, 14
Cyclophosphamide mono			
Cyclophosphamide	1,000 mg/qm	IV	1, 2
G-CSF	5–10 µg/kg bw[1]	IV	9, 10, 11, 12, 13, 14

G-CSF, granulocyte colony-stimulating factor; IV, intravenous; PO, per os; SC, subcutaneous. [1] G-CSF 5 µg/kg body weight was applied after VCD and 10 µg/kg body weight was applied after Dara-VTD.

therapy [9–11]. Hence, a maximum of three HDCT/ASCTs may be performed in a single patient. The prerequisite for this approach is the successful collection of at least three peripheral blood stem cell (PBSC) transplants, each containing a sufficient number of $CD34^+$ PBSCs (usually $\geq 2.0 \times 10^6$/kg body weight [bw]) [2, 12]. Application of granulocyte colony-stimulating factor (G-CSF) with or without prior chemotherapy is necessary for PBSC mobilization [13]. Prior to mobilization, standard-of-care for transplant-eligible patients are triplet therapies comprising a proteasome inhibitor, dexamethasone, and either cyclophosphamide or an immunomodulatory drug (IMiD) [3, 8, 14, 15]. While some factors such as radiotherapy, higher age, and melphalan are associated with poor PBSC mobilization, data on newer agents are often contradictory [16–20]. Some novel agents such as IMiDs might interfere with PBSC mobilization and collection [18–24]. The addition of an anti-CD38 antibody to an established triplet protocol improves efficacy but might hamper PBSC collection as shown in the phase 3 CASSIOPEIA trial [25]. However, only data on overall collection results but not on other important surrogate markers such leukapheresis (LP) delay, number of LP sessions, and the use of the chemokine receptor antagonist plerixafor are available so far. Our study evaluates detailed PBSC mobilization and collection metrics in NDMM after induction with daratumumab, bortezomib, thalidomide, and dexamethasone (Dara-VTD) versus bortezomib, cyclophosphamide, and dexamethasone (VCD).

Methods

Patients

For this study, $n = 119$ consecutive patients with NDMM who underwent PBSC collection at the University Hospital Heidelberg after induction therapy with Dara-VTD or VCD between 2021 and 2022 were included. LP collection metrics were routinely recorded upon LP sessions, such as peripheral blood (PB) $CD34^+$ cell count, PB leukocyte counts, amount of processed blood, PBSC collection result per LP session, G-CSF dosing, plerixafor application, and complete blood count prior to and post LP. Other patient characteristics were extracted from routine medical records. The study is in accordance with the most recent version of the Declaration of Helsinki.

Induction Treatment and PBSC Mobilization/Collection

Patients with NDMM underwent a median of 4 cycles of either VCD (21 days) or Dara-VTD (28 days). The choice of induction therapy was not based on disease characteristics. PBSC mobilization and collection were performed after the fourth induction cycle in 118/119 patients. Response assessment was conducted at least after one and 4 cycles. Mobilization chemotherapy was applied to almost all patients, comprising cyclophosphamide, adriamycin, and dexamethasone (CAD). In case of reduced ejection fraction or a pre-existing cardiac condition (myocardial infarction, coronary heart disease, cardiac bypass surgery, etc.), patients were subjected to cyclophosphamide, 13% of all patients in our cohort. G-CSF was applied on days 9–14. On day 14, the first PB $CD34^+$ cell measurement was conducted. LP was initiated if the PB $CD34^+$ cell count exceeded 10/µL. In case of tolerable safety, the following LPs were conducted until collection of three transplants comprised $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg bw. In case of collection failure, reflected by insufficient PB CD34+ cell counts or insufficient collection, preemptive or rescue mobilization with plerixafor was applied [26, 27]. In short, PB $CD34^+$ <10/µL after continued G-CSF stimulation until the day after the first planned measurement triggered preemptive plerixafor application. At PB $CD34^+$ 10/µL–20/µL, plerixafor was used per treating physician's discretion. Rescue mobiliza-

Table 2. Patients' characteristics at first diagnosis

Variable	Overall cohort		Dara-VTD (28 days/cycle)		VCD (21 days/cycle)		*p* value
	n	%	*n*	%	*n*	%	
Patients	119	100	58	100	61	100	/
Gender							
Male	70	59	35	60	35	57	0.852
Female	49	41	23	40	26	43	
Diagnosis							
MM	119	100	58	100	61	100	/
Median age at diagnosis, years (range)	59	(34–71)	60	(34–69)	59	(35–71)	**0.023**
Heavy chain type							
IgG	68	57	36	62	32	52	0.474[a]
IgA	25	21	12	21	13	21	
IgM	0	0	0	0	0	0	
IgD	0	0	0	0	0	0	
Light chain only	25	21	9	16	16	26	
Nonsecretory	1	1	1	2	0	0	
Light chain type							
Lambda	35	29	17	29	18	30	0.918[b]
Kappa	83	70	40	69	43	70	
Double gammopathy	0	0	0	0	0	0	
Nonsecretory	1	1	1	2	0	0	
ISS stage							
I	47	39	28	48	19	31	0.167
II	26	22	14	24	12	20	
III	34	29	13	22	21	34	
NA	11	9	3	5	8	13	
r-ISS stage							
1	20	17	12	21	8	13	0.256
2	47	39	26	45	21	34	
3	17	14	7	12	10	16	
NA	35	29	13	22	22	36	
Cytogenetic profile							
High risk	43	36	22	38	21	34	0.457
Standard risk	59	50	32	55	27	44	
NA	17	14	4	7	13	21	

Ig, immunoglobulin; ISS, International Staging System; MM, multiple myeloma; NA, not available; PBSC, peripheral blood stem cell; SD, standard deviation. [a] IgG versus IgA, IgM versus light chain only. [b] Lambda versus Kappa.

tion was applied if less than 2.0×10^6 $CD34^+$ cells/kg bw were collected during first LP (LP1). In case of higher age or suspected inability for relapse transplant, collection goal was reduced to one or two transplants at the attending physician's discretion. In the VCD group, 5/61 patients were subjected to 1–4 additional induction cycles since ASCT had to be postponed due to restrictions caused by the COVID-19 pandemic. Detailed information on induction and mobilization protocols is presented in Table 1.

Statistics

Descriptive statistics were performed using SPSS (v27). Data are depicted as dot plots with absolute numbers and boxplots with whiskers (median, interquartile range, minimum/maximum whiskers) or boxplots with Tukey whiskers without absolute numbers. Proportions of patients were depicted as pie diagrams. For univariate analysis in metric datasets, two-sided unpaired *t*-tests and Mann-Whitney U tests were performed. For univariate analysis in nonmetric datasets, Fisher's exact test was used. Multivariable logistic regression analysis was performed using SPSS (v27). *p* values < 0.05 were considered statistically significant.

Results

Patients' Characteristics

In this work, $n = 119$ patients were included, 70 (59%) of whom were male (Table 2). All patients were treated for symptomatic MM according to International Myeloma Working Group criteria [28]. The median age at diagnosis was 59 years (range 34–71). 68 patients (57%) had IgG and 25 (21%) IgA as monoclonal protein. Bence Jones myeloma was present in 25 patients (21%). 83 patients (70%) exhibited kappa light chain restriction, 1 patient (1%) had nonsecretory MM. 47 (39%) patients exhibited ISS stage 1, 26 (22%) stage 2, and 34 (29%) stage 3. High-risk cytogenetics were found in 43 patients (36%). 58 patients (49%) were treated with Dara-VTD and 61 patients (51%) were treated with VCD. Patients' characteristics were well balanced between the two groups, with

Table 3. First-line treatment and PBSC mobilization

Variable	Overall cohort		Dara-VTD (28 days/cycle)		VCD (21 days/cycle)		*p* value
	n	%	*n*	%	*n*	%	
Patients	119	100	58	100	61	100	/
Remission post-induction							
CR	0	0	0	0	0	0	0.010[a]
nCR	25	21	9	16	16	26	
VGPR	46	39	29	50	17	28	
PR	41	34	16	28	25	41	
SD	3	3	0	0	3	5	
MR	1	1	1	2	0	0	
PD	0	0	0	0	0	0	
NA	3	3	3	5	0	0	
Number of cycles prior to mobilization							
2	1	1	0	0	1	2	0.999
4	118	99	58	100	60	98	
Number of cycles prior to transplantation							
4	114	96	58	100	56	92	0.178
5	3	3	0	0	3	5	
6	1	1	0	0	1	2	
8	1	1	0	0	1	2	
Mobilization regimen							
CAD	103	87	52	90	51	84	0.584
Cyclophosphamide	15	13	6	10	9	15	
G-CSF only	1	1	0	0	1	2	
Collection target							
3 transplants	110	92	57	98	53	87	**0.049**
2 transplants	7	6	1	2	6	10	
1 transplant	2	2	0	0	2	2	
Plerixafor application							
Yes	31	26	19	33	12	20	0.143
No	88	74	39	67	49	80	
Plerixafor doses							
Plerixafor doses per 100 patients	41		47		36		0.174
Patients with distinct number of doses							
0	88	74	39	67	49	80	**0.031**
1	20	17	15	26	5	8	
≥2	11	9	4	7	7	11	

CAD, cyclophosphamide, doxorubicin, dexamethasone; CR, complete response; G-CSF, granulocyte colony-stimulating factor; HDCT, high-dose chemotherapy; MR, minimal response; NA, not available; nCR, near complete response; PBSC, peripheral blood stem cell; PD, progressive disease; PR, partial response; Dara-VTD, daratumumab, bortezomib, thalidomide, dexamethasone; SD, stable disease; VGPR, very good partial response; VCD, bortezomib, cyclophosphamide, dexamethasone. [a] CR and nCR versus VGPR versus PR or worse.

a difference in median age at diagnosis (57 years in Dara-VTD vs. 60 years in VCD, $p = 0.023$). All other baseline patient characteristics were equally distributed among groups. Remission after induction therapy was superior in the Dara-VTD group (very good partial response and nCR 66% vs. 54%, $p = 0.011$).

PBSC Mobilization Metrics

Mobilization was induced with cyclophosphamide, adriamycin, dexamethasone chemotherapy and G-CSF in 103 patients (87%), with cyclophosphamide and G-CSF in 15 (13%) and with G-CSF only in 1 patient (1%) (Table 3). G-CSF was applied at 10 versus 5 μg/kg bw/day in Dara-VTD versus VCD. On day 14 after initiation of mobilization therapy, 76% of the Dara-VTD cohort and 62% of the VCD cohort surpassed the threshold of 10/μL $CD34^+$ cells in the PB and underwent LP (Fig. 1a). Mean PB $CD34^+$ cell count at LP1 was lower in the Dara-VTD compared to VCD group (65 vs. 106/μL) (Fig. 1b). Accordingly, $CD34^+$ cell collection at LP1 was lower after Dara-VTD (5.5 vs. 8.3 $CD34^+$ cells $\times 10^6$/kg) (Fig. 1c). Patients in the Dara-VTD group required a higher median number of LP sessions (2 vs. 1), and only 31% completed collection after LP1 (vs. 72% in the VCD group) (Fig. 1d, e).

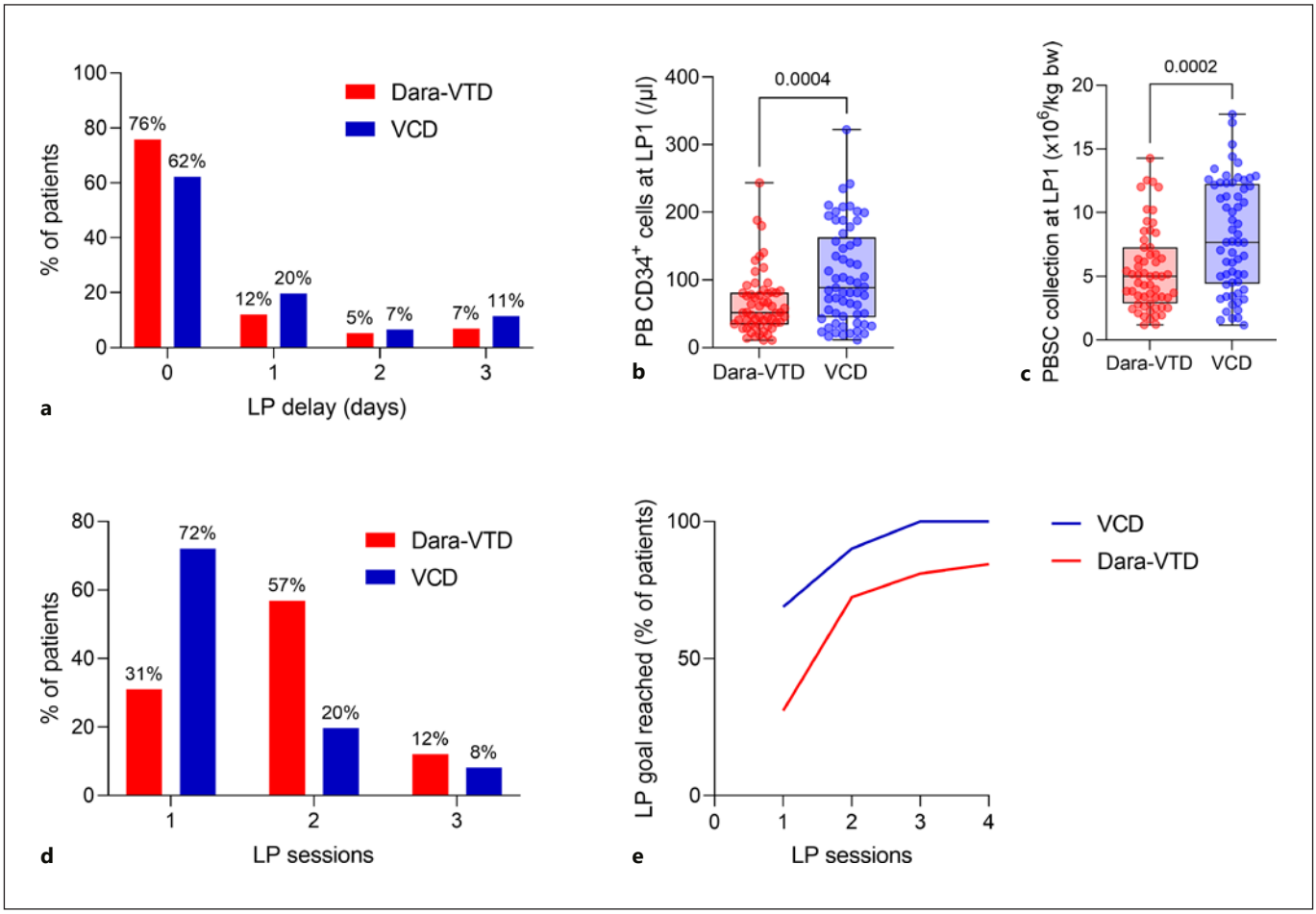

Fig. 1. PBSC mobilization metrics. **a** Time difference (days) between planned and actual date of LP1. **b** PBSC collection ($CD34^+$ cells $\times 10^6$/kg bw) upon the LP1 session. **c** PB $CD34^+$ cell count (/µL) after mobilization. **d** Number of LP sessions until collection goal (% of subgroup). **e** Percentage of patients reaching collection goal after respective LP.

Utilization of Plerixafor

In patients with impaired mobilization (LP delay ≥1 day or insufficient LP1), the chemokine receptor antagonist plerixafor was applied. Overall, 33% of patients in the Dara-VTD group and 21% of patients in the VCD group received plerixafor (Fig. 2a). In 9% of patients, plerixafor was applied more than once, resulting in a cumulated dose per 100 patients of 47 versus 36 in the Dara-VTD and the VCD group, respectively (Fig. 2b). $CD34^+$ cell PB mobilization after plerixafor application was equal in both groups, with a two-fold increase of PBSC (Fig. 2c, $p = 0.66$). Likewise, $CD34^+$ cell collection results of second LP, after the administration of plerixafor, improved in both groups (Fig. 2d).

Overall PBSC Collection Outcomes

The PBSC collection outcome is given in Table 4. Overall PBSC collection was 8.9×10^6 $CD34^+$ cells/kg bw in the whole analyzed cohort, with a lower collection result in the Dara-VTD and VCD cohort (8.4 vs. 9.6×10^6 $CD34^+$ cells per kg bw, $p = 0.02$) (Fig. 2e). Absolute collection failure (overall collection $<2 \times 10^6$/kg bw $CD34^+$ cells) did not occur; however, the collection target was reached in 79% of patients in the Dara-VTD group and 97% of patients in the VCD group (Fig. 2f). All patients were subsequently subjected to HDCT/ASCT.

Multivariate Analysis

Multivariable logistic regression analysis regarding the outcome variables' successful collection of three transplants at LP1, PB $CD34^+$ cells at LP 1 (>50/µL vs. <50/µL), use of plerixafor (yes vs. no), and number of LP sessions (>1 vs. 1) was performed (Table 5). Induction with VCD significantly correlated with collection success at LP1 (odds ratio [OR] = 4.46, $p < 0.01$), higher PB $CD34^+$ cells/µL at LP1 (OR = 0.5.79, $p < 0.01$) as well as lower use of plerixafor (OR = 0.17, $p < 0.01$) and lower number of LP sessions (OR = 0.19, $p < 0.01$). Interestingly, mobilization

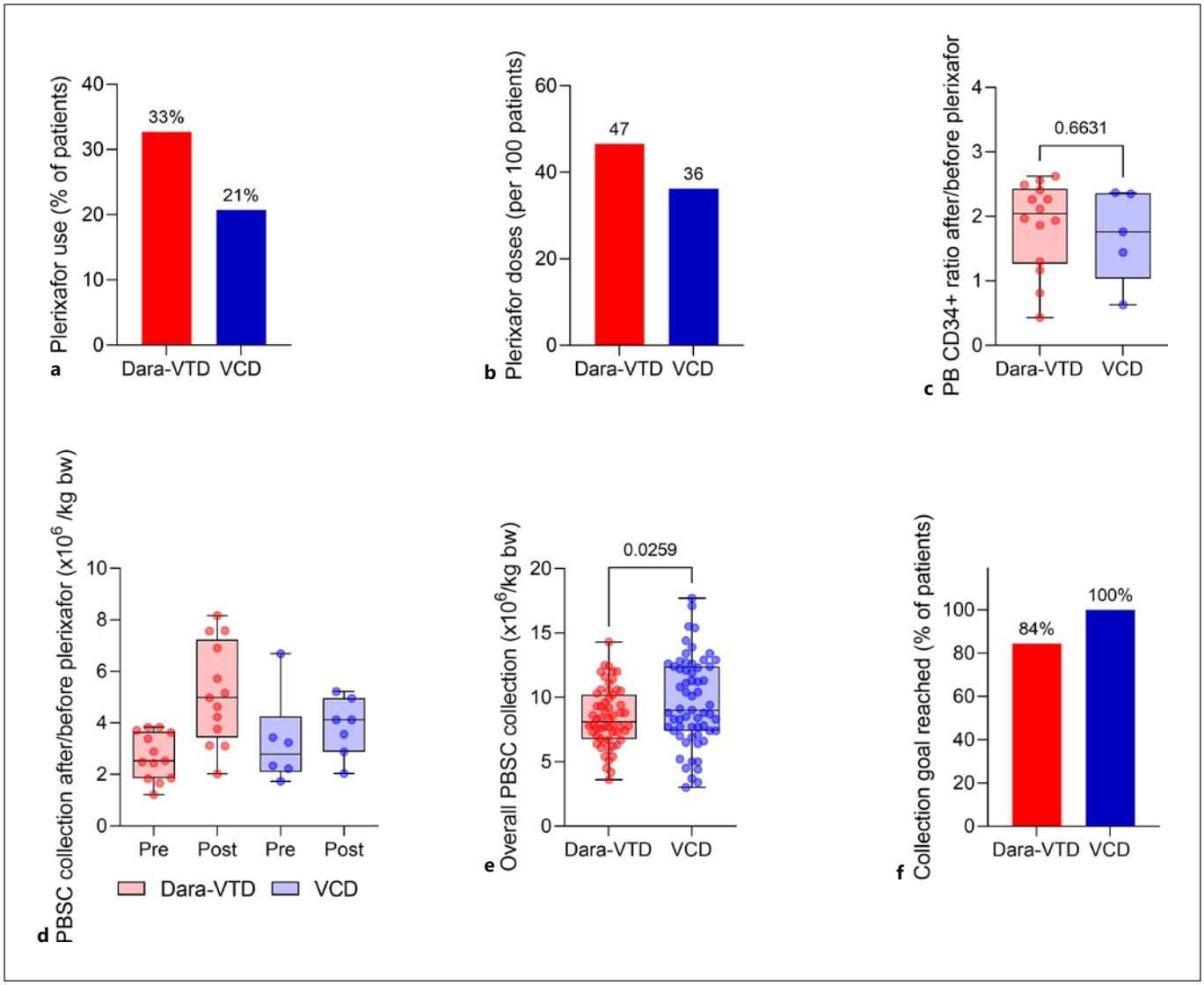

Fig. 2. PBSC collection results. **a** Plerixafor use due to poor mobilization (% of subgroup). **b** Plerixafor doses per 100 patients that underwent PBSC collection. **c** Ratio of PB CD34$^+$ cell count after and before plerixafor application. **d** PBSC collection (CD34$^+$ cells $\times 10^6$/kg bw) without plerixafor versus after plerixafor. **e** Overall PBSC collection results (CD34$^+$ cells $\times 10^6$/kg bw). **f** Collection goal reached after all LP sessions (% of subgroups).

therapy with cyclophosphamide correlated with higher utilization of plerixafor (OR = 11.02, $p < 0.01$). Furthermore, patients exhibiting high-risk cytogenetics needed an increased number of LP sessions (OR 2.65, $p = 0.04$).

Discussion

This study reports on PBSC mobilization and collection metrics in patients with NDMM after induction therapy with VCD or Dara-VTD. While data on overall PBSC collection in the CASSIOPEIA trial are available, this study provides more detailed analyses on the impact of different induction regimens on PBSC collection.

The study has various assets: patients' characteristics including cytogenetics (available in 86%) and ISS stadium (91%) are available for a vast majority of patients. Most characteristics are equally distributed among groups, except for higher median age at diagnosis in VCD. Due to the quality of data acquisition, multivariate analysis was feasible, which validated the findings seen in the univariate analysis. Both VCD and Dara-VTD protocols are approved for NDMM by the EMA and are widely used in different countries [29]. By analyzing additional surrogate markers such as LP sessions, LP delay, and PB CD34$^+$ cell count, a broader picture of mobilization success and mobilization failure is drawn. Since LP duration and blood flow are often based on PB CD34$^+$

Table 4. PBSC collection

Variable	Overall cohort		Dara-VTD (28 days/cycle)		VCD (21 days/cycle)		*p* value
	n	%	*n*	%	*n*	%	
Patients	119	100	58	100	61	100	/
Prolonged mobilization							
Median delay, days (range)	0 (0–22)		0 (0–22)		0 (0–21)		0.144
Delayed LP							
0, days	82	69	44	76	38	62	**0.001**[a]
1 day	20	17	7	12	13	21	
≥2 days	17	14	7	12	10	16	
Blood count at LP1							
Mean leukocyte count/nL (SD)	24 (14)		28 (15)		20 (12)		**0.003**
Mean PB $CD34^+$ cells/µL (SD)	86 (64)		65 (46)		106 (72)		**0.001**
LP1 session							
Mean $CD34^+$ cells $\times 10^6$/kg bw (SD)	6.9 (4.1)		5.5 (3.2)		8.3 (4.5)		**0.001**
Mean processed blood volume, L (SD)	15.5 (3.8)		16.3 (3.4)		14.7 (4.0)		0.022
Overall PBSC collection result							
Mean $CD34^+$ cells $\times 10^6$/kg bw (SD)	9.0 (3.0)		8.4 (2.4)		9.6 (3.4)		**0.026**
LP sessions							
Median, *n* (range)	1 (1–6)		2 (1–6)		1 (1–3)		**0.001**
LP sessions							
1	60	50	18	31	42	69	**0.001**[b]
2	46	39	33	57	13	21	
3	11	9	5	9	6	10	
≥4	2	2	2	3	0	0	
LP collection target reached	105	88	46	79	59	97	**0.049**
3 transplants	97	82	45	78	52	85	
2 transplants	18	15	12	21	6	10	
1 transplant	4	3	1	2	3	2	

bw, body weight; Dara-VTD, daratumumab, bortezomib, thalidomide, dexamethasone; L, liter; LP, leukapheresis; PBSC, peripheral blood stem cell; SD, standard deviation; VCD, bortezomib, cyclophosphamide, dexamethasone. [a] Zero days versus 1 day versus 2 or more days. [b] One LP versus 2 LPs versus ≥3 LPs.

Table 5. Multivariable analyses of PBSC mobilization/collection outcome parameters

Variable	Collection of 3 transplants at LP1 (yes vs. no)		$CD34^+$ cells in PB at LP1 (>50/µL vs. ≤50/µL)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender (female vs. male)	0.63 (0.26, 1.57)	0.32	0.83 (0.33, 2.12)	0.70
Age (>60 vs. ≤60 years)	0.49 (0.18, 1.36)	0.17	0.30 (0.10, 0.89)	**0.03**
High-risk cytogenetics (yes vs. no)	0.51 (0.20, 1.30)	0.16	0.80 (0.31, 2.11)	0.65
ISS (3 vs. 1–2)	1.00 (0.38, 2.72)	0.98	0.54 (0.19, 1.55)	0.25
Mobilization therapy (C vs. CAD)	0.36 (0.07, 1.82)	0.22	0.28 (0.06, 1.32)	0.11
Induction (VCD vs. Dara-VTD)	4.46 (1.67, 11.91)	**<0.01**	4.79 (1.63, 14.04)	**<0.01**
Remission after induction (≥VGPR vs. <VGPR)	1.03 (0.40, 2.67)	0.95	1.01 (0.36, 2.79)	0.99
Variable	Plerixafor (yes vs. no)		LP sessions (>1 vs. 1)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender (female vs. male)	2.03 (0.66, 6.28)	0.22	1.10 (0.44, 2.75)	0.84
Age (>60 vs. ≤60 years)	3.78 (0.98, 14.59)	0.05	1.14 (0.42, 3.10)	0.81
High-risk cytogenetics (yes vs. no)	1.62 (0.50, 5.25)	0.43	2.65 (1.02, 6.90)	**0.04**
ISS (3 vs. 1–2)	0.88 (0.24, 3.30)	0.85	1.38 (0.49, 3.86)	0.54
Mobilization therapy (C vs. CAD)	11.02 (1.91, 63.65)	**<0.01**	2.73 (0.53, 13.97)	0.23
Induction (VCD vs. Dara-VTD)	0.17 (0.05, 0.62)	**<0.01**	0.19 (0.07, 0.52)	**<0.01**
Remission after induction (≥VGPR vs. <VGPR)	1.17 (9.32, 4.25)	0.81	1.02 (0.39, 2.68)	0.97

bw, body weight; C, cyclophosphamide; CAD, cyclophosphamide, adriamycin, dexamethasone; CI, confidence interval; Dara-VTD, daratumumab, lenalidomide, bortezomib, dexamethasone; ISS, International Staging System; LP, leukapheresis; PB, peripheral blood; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

cell count, LPs might be terminated earlier after assumed collection success [30]. This self-limitation hampers the validity of overall collection result as sole endpoint. The quantification of plerixafor doses is important to evaluate cost-effectiveness. In this study, we showed that inferiority of PBSC collection after Dara-VTD versus VCD cannot be fully compensated with plerixafor. However, all patients in our cohort collected at least one sufficient transplant, and all patients were subjected to HDCT/ASCT.

The study has some limitations. First, retrospective analyses may not be ideally suited to fully understand the clinical question presented here. The use of an increased G-CSF dose in the Dara-VTD group (10 vs. 5 μg/kg bw) might influence the collection outcome and might account for a quicker but less sustained stem cell mobilization (as mirrored by lower rates of LP delay). Second, since both daratumumab and thalidomide are part of the Dara-VTD group, the causative agent may not be identified easily. However, a recent analysis reports similar collection results after VTD versus VCD in a small cohort [31]. While sufficient PBSC collection was feasible in a majority of patients treated with Dara-VTD, increased LP numbers and increased use of plerixafor might have had an impact on quality of life. However, no data are available in this study. Our retrospective analysis is not powered to compare response rates and survival. Long-term analyses on duration of response after HDCT/ASCT with Dara-VTD are needed to further support treatment decisions. While for a majority of patients in the Dara-VTD group PBSC collection goals were met after application of plerixafor, the financial impact should be taken into account [32].

Both Dara-VTD and VCD are standard-of-care in transplant-eligible patients with NDMM. However, VTD showed superior response parameters compared to VCD [33]. Furthermore, the addition of daratumumab to VTD led to improved response parameters and survival [25]. Additionally, other quadruplet therapies are under evaluation in NDMM. In the phase 2 GRIFFIN study, daratumumab-VRD showed remarkable results [34]. However, Laurent et al. [35] report on impaired PBSC collection after VRD versus VTD. One could thus speculate that Dara-VRD might lead to even lower PBSC yields compared to Dara-VTD. Further research on PBSC collection after Dara-VRD is needed.

The data on the impact of IMiDs on PBSC collection are contradictory but favor a negative impact. Breitkreutz et al. showed inferior collection results in NDMM patients treated with thalidomide, doxorubicin, and dexamethasone compared with vincristine, doxorubicin, and dexamethasone [36]. In contrast, Ghobrial et al. did not find significant differences in PBSC collection yield with thalidomide [37].

Addition of anti-CD38 antibodies to triplet induction therapies might influence PBSC collection results since CD38 is expressed on bone marrow precursor cells [38]. However, the abundance of CD38 is higher in myeloma cells compared to stem cells [39]. In line with this observation, the anti-CD38 antibody isatuximab did not induce lysis of stem cells in an in vitro study by Zhu et al. [40] while exerting efficient killing of MM cells. Clinical data on the influence of CD38 antibodies on PBSC collection are rare [41]. While overall collection results were reduced after Dara-VTD versus VTD [25], it was unclear whether application of plerixafor may help overcome this hurdle. Our study provides evidence that plerixafor and higher doses of G-CSF (10 vs. 5 μg/kg bw/day) cannot fully compensate for the impact of daratumumab and thalidomide on PBSC collection metrics.

Furthermore, the increased number of LP sessions as well as the increased utilization of plerixafor in the Dara-VTD group significantly increase the financial impact of stem cell collection in these patients. Cost-effectiveness of Dara-VTD should be further discussed, as both direct and indirect costs are increased when compared to VCD.

In order to validate our findings, additional studies, e.g., comparing VCD and daratumumab-VCD may be helpful. Furthermore, data on stem cell collection after isatuximab-based quadruplet induction within the GMMG-HD7 study (isatuximab-RVd vs. RVd) may help to understand the impact of anti-CD38 mAb therapy on stem cell yield. In summary, PBSC collection after daratumumab-VTD is impaired when compared to PBSC collection after VCD induction.

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Statement of Ethics

The retrospective study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty, Heidelberg University.

Conflict of Interest Statement

The first authors and all coauthors confirm that there are no potential conflicts of interest to disclose, except the following. Joseph Kauer: Honoraria: AstraZeneca. Sandra Sauer: travel grants or honoraria for presentations for Celgene, BMS, Janssen, Takeda, and Amgen. Katharina Kriegsmann: research funding and honoraria from Sanofi. A.S. received travel grants from Hexal and Jazz

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Author Contributions

Conceptualization: Sandra Sauer, Katharina Kriegsmann, and Joseph Kauer; methodology: Anita Schmitt; formal analysis, visualization, and writing – original draft preparation: Joseph Kauer and Katharina Kriegsmann; investigation: Joseph Kauer and Cathleen Nientiedt; resources, project administration, and supervision: Sandra Sauer and Katharina Kriegsmann; data curation: Cathleen Nientiedt, Joseph Kauer, and Anita Schmitt; writing – review and editing: Sandra Sauer, Marc-Steffen Raab, and Carsten Müller-Tidow; funding acquisition: not applicable. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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