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Impact of Clinical Parameters and Induction Regimens on Peripheral Blood Stem-Cell Mobilization and Collection in Multiple Myeloma Patients

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Multiple myeloma · Leukapheresis · Stem cell mobilization · Stem cell collection · Peripheral blood stem cells · CD34

Abstract

Introduction: High-dose chemotherapy (HDCT) followed by autologous blood stem-cell transplantation (ABSCT) remains the standard consolidation therapy for newly diagnosed eligible multiple myeloma (MM) patients. As a prerequisite, peripheral blood stem cells (PBSCs) must be mobilized and collected by leukapheresis (LP). Many factors can hamper PBSC mobilization/collection. Here, we provide a comprehensive multiparametric assessment of PBSC mobilization/collection outcome parameters in a large cohort. ***Methods:*** In total, 790 MM patients (471 [60%] male, 319 [40%] female) who underwent PBSC mobilization/collection during first-line treatment were included. Evaluated PBSC mobilization/collection outcome parameters included the prolongation of PBSC mobilization, plerixafor administration, number of LP sessions, and overall PBSC collection goal/result. ***Results:*** 741 (94%) patients received cyclophosphamide/adriamycin/dexamethasone (CAD) and granulocyte-colony-stimulating factor (G-CSF) mobilization. Plerixafor was administered in 80 (10%) patients. 489 (62%) patients started LP without delay. 530 (67%) patients reached the PBSC collection goal at the first LP session. The mean overall PBSC collection result was 10.3 (standard deviation [SD] 4.4) × 10^6 $CD34^+$ cells/kg. In a multiparametric analysis, variables negatively associated with PBSC mobilization/collection outcomes were female gender, age >60 years, an advanced ISS stage, and local radiation pre-/during induction, but not remission status postinduction. Notably, the identified risk factors contributed differently to each PBSC mobilization/collection outcome parameter. In this context, compared to all other induction regimens, lenalidomide-based induction with/without antibodies negatively affected only the number of LP sessions required to reach the collection goal, but no other PBSC mobilization/collection outcome parameters. In contrast, the probability of reaching a high collection goal of ≥6 × 10^6 $CD34^+$ cells/kg body weight was higher after lenalidomide-based induction compared to VCD/PAD or VAD – taking into account – that a higher G-SCF dosage was given in approximately one-third of patients receiving lenalidomide-based induction with/without antibodies. ***Conclusion:*** Considering the identified risk factors in the clinical setting can contribute to optimized PBSC mobilization/collection. Moreover, our study demonstrates the necessity for a differentiated evaluation of PBSC mobilization/collection outcome parameters.

Introduction

Although the depth and duration of the response achieved with state-of-the-art induction regimens challenge this concept, high-dose chemotherapy (HDCT)

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followed by autologous blood stem-cell transplantation (ABSCT) is still considered the standard of care for eligible multiple myeloma (MM) patients [1]. Initially established as a single therapy, subsequent studies found a survival benefit with tandem HDCT/ABSCT in first-line treatment, particularly in patients who do not achieve at least a partial response [2–6]. Further trials demonstrated that salvage HDCT/ABSCT may be advantageous in MM patients who relapse after 1 year of remission following prior HDCT/ABSCT [7–9]. Consequently, up to three HDCT/ABSCTs can be considered over the course of treatment.

As a prerequisite, peripheral blood stem cells (PBSCs), which are the primary source of hematopoietic stem cells in this setting, must be collected and stored until reinfusion [10, 11]. PBSCs are mobilized with chemotherapy and granulocyte-colony-stimulating factor (G-CSF) and collected by leukapheresis (LP) [12]. Generally, up to three sufficient PBSC grafts ($\geq 2.0 \times 10^6$ CD34+ cells/kg body weight [bw] per graft) can be collected [13, 14].

Many factors, such as age and previous extensive chemo- or radiation therapy, may hamper PBSC mobilization and collection [15–19]. However, most previous studies are not cohesive and do not provide a multiparametric analysis. Moreover, these analyses mainly focus on the $CD34^+$ cell collection yield and disregard other outcome parameters of PBSC mobilization and collection, such as the prolonged PBSC mobilization, need for plerixafor administration, number of LP sessions required to reach the collection goal, and different collection goal cutoffs. In the current analysis, we provide a comprehensive multiparametric evaluation of MM disease and treatment parameters, focusing on the detailed assessment of PBSC mobilization and collection outcome parameters.

Materials and Methods

Patient Selection and Data Acquisition

All MM patients who underwent PBSC mobilization and collection in the Department of Hematology, Oncology and Rheumatology at the University Hospital Heidelberg during first-line treatment from 2007 to 2009 and 2015 to 2019 were included. These two periods represent conventional and new induction regimens, allowing the present study to investigate their influence on PBSC mobilization and collection. Clinical parameters at first diagnosis (FD), first-line therapy induction regimens, and outcome parameters, such as remission status, were collected retrospectively from medical records. PBSC mobilization and collection outcome parameters, such as the prolongation of PBSC mobilization, plerixafor administration, number of LP sessions, and PBSC collection goal and result, were also collected retrospectively. Retrospective data analysis was approved by the Ethics Committee of the Medical Faculty of Heidelberg University.

Induction Regimens and PBSC Mobilization/Collection

The administered induction regimens were, by group: (a) lenalidomide-based with/without antibody ([elotuzumab-] bortezomib, lenalidomide, dexamethasone [20] [isatuximab-] lenalidomide, bortezomib, and dexamethasone [21]); (b) bortezomib, cyclophosphamide, dexamethasone [VCD] [22] and bortezomib, doxorubicin, and dexamethasone (PAD) [22]; (c) vincristine, doxorubicin, and dexamethasone (VAD) [23], and (d) other (including thalidomide, doxorubicin, and dexamethasone [TAD] [24] and patients who received several induction regimens).

PBSC mobilization and collection were performed according to an established and evaluated procedure as described previously [25, 26]. The minimum requirement for one transplant was defined as $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg. The overall collection goal was defined as three sufficient transplants. The prolongation of PBSC mobilization, plerixafor administration, and number of required LP sessions to reach the collection goal, and overall collected $CD34^+$ cells/kg were evaluated as key metrics for PBSC mobilization and collection. The prolongation of PBSC mobilization was defined as the difference in days between the planned and actual dates of LP initiation due to low $CD34^+$ cell concentration in the peripheral blood. In detail, the first day of mobilization chemotherapy application was assumed to be day 1; cyclophosphamide/adriamycin/dexamethasone was administered at 4 days (day 1 – day 4); G-SCF was initiated at day 9 for 4 days; and CD34+ cell assessment and LP were planned for day 13. In case of insufficient peripheral blood CD34+ cell concentration, G-CSF administration was prolonged. The variable prolongation of PBSC mobilization therefore indicates whether additional G-CSF administration days were required to reach a sufficient peripheral blood $CD34^+$ cell concentration for the initiation of LP. Plerixafor was administered in cases of insufficient PBSC mobilization (peripheral blood $CD34^+$ cell concentration <10 [−20]/μL; preemptive administration) or insufficient PBSC collection (<1/3 of PBSC collection goal reached at the first LP session; rescue administration).

Statistical Analysis

Statistical analysis was performed with R-Studio (R version 4.0.0, 2020-04-24). Descriptive statistics were performed for the overall cohort according to the type of induction therapy: "lenalidomide-based with/without antibodies," "VCD/PAD," "VAD," and "other." Data are presented as absolute numbers and percentages, medians and ranges (defined as minimum–maximum), as well as means and standard deviations (SD) where appropriate. To investigate the influence of clinical and treatment parameters (independent variables: gender, age at FD, International Staging System [ISS] stage at FD, induction therapy, local radiation pre-/during induction, remission status postinduction) on PBSC mobilization and collection outcome parameters (dependent variables: prolonged mobilization, plerixafor administration, number of LP sessions, collection goal of $\geq 6 \times 10^6$ $CD34^+$ cells/kg, collection goal of $\geq 4 \times 10^6$ $CD34^+$ cells/kg, overall CD34+ cells collection result), multivariable logistic and linear regression models were used. The results are presented as odds ratio (OR), 2.5%–97.5% confidence interval ($CI_{2.5\%–97.5\%}$) and estimate, and standard error (SE). A p value ≤ 0.05 was defined as statistically significant.

Results

Patients Characteristics at First Diagnosis and Induction Treatment

Overall, 790 patients (471 [60%] male, 319 [40%] female) were analyzed. The average age at FD was 58 (SD 8) years. 355 (45%), 167 (21%), and 178 (23%) were diagnosed with ISS stage I, II, and III, respectively. Patient characteristics at FD grouped by the type of induction

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Table 1. Patient characteristics at FD

Variable	Overall cohort		Induction therapy							
			Lenalidomide-based with/without antibody		VCD/PAD		VAD		Other	
N	790		187		403		102		98	
Gender (%)										
Male	471	(60)	120	(64)	241	(60)	57	(56)	54	(55)
Female	319	(40)	67	(36)	162	(40)	45	(44)	44	(45)
Age, mean years (SD)	58	(8)	58	(8)	59	(8)	60	(9)	57	(9)
Heavy chain type (%)										
IgG	485	(61)	120	(64)	226	(56)	69	(68)	70	(71)
IgA	150	(19)	36	(19)	88	(22)	15	(15)	11	(11)
IgM	4	(1)	2	(1)	2	(0)	0	(0)	0	(0)
IgD	11	(1)	0	(0)	10	(2)	0	(0)	1	(1)
IgE	1	(0)	1	(1)	0	(0)	0	(0)	0	(0)
Double gammopathy	6	(1)	2	(1)	3	(1)	1	(1)	0	(0)
Light chain only	124	(16)	26	(14)	69	(17)	14	(14)	15	(15)
Nonsecretory	9	(1)	0	(0)	5	(1)	3	(3)	1	(1)
Light chain type (%)										
Lambda	285	(36)	66	(35)	153	(38)	30	(29)	36	(37)
Kappa	490	(62)	119	(64)	242	(60)	68	(67)	61	(62)
Double gammopathy	6	(1)	2	(1)	3	(1)	1	(1)	0	(0)
Nonsecretory	9	(1)	0	(0)	5	(1)	3	(3)	1	(1)
Salmon and Durie stage (%)										
IA	50	(6)	26	(14)	20	(5)	0	(0)	4	(4)
IB	1	(0)	0	(0)	1	(0)	0	(0)	0	(0)
IIA	53	(7)	9	(5)	27	(7)	10	(10)	7	(7)
IIB	2	(0)	0	(0)	2	(0)	0	(0)	0	(0)
IIIA	591	(75)	144	(77)	288	(71)	83	(81)	76	(78)
IIIB	85	(11)	6	(3)	60	(15)	9	(9)	10	(10)
NA	8	(1)	2	(1)	5	(1)	0	(0)	1	(1)
ISS stage (%)										
I	355	(45)	103	(55)	158	(39)	48	(47)	46	(47)
II	167	(21)	44	(24)	92	(23)	17	(17)	14	(14)
III	178	(23)	31	(17)	103	(26)	16	(16)	28	(29)
NA	90	(11)	9	(5)	50	(12)	21	(21)	10	(10)

ISS, International Staging System; NA, not available; PAD, bortezomib, doxorubicin, dexamethasone; SD, standard deviation; VAD, vincristine, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone.

therapy are presented in Table 1. Lenalidomide-based induction therapy with/without antibodies, VCD/PAD, VAD, and other induction regimens were administered to 187, 403, 102, and 98 patients, respectively. A median of 4 (2–9) cycles of induction therapy were administered. 179 (23%) patients received local radiation pre-/during induction therapy, and 349 (44%) patients reached a very good partial response or better after induction therapy. Induction therapy and postinduction remission status details are presented in Table 2.

PBSC Mobilization and Collection

741 (94%) patients received CAD and G-CSF as mobilization therapy. Plerixafor administration was performed in 80 (10%) patients. Although 489 (62%) patients started LP without delay, the remaining patients required a prolonged G-CSF administration to reach a sufficient PB $CD34^+$ cell concentration. At the first LP session, the mean PB $CD34^+$ cell concentration was 8.7 (SD 4.9)/μL, and 530 (67%) patients reached the PBSC collection goal. However, 260 (33%) patients required more than one LP session to reach the collection goal. The mean overall PBSC collection result was 10.3 (SD 4.4) $\times 10^6$ CD34+ cells/kg. Detailed information on PBSC mobilization and collection is provided in Table 3.

Impact of Clinical Parameters and Induction Treatment on PBSC Mobilization/Collection

To investigate the influence of clinical and treatment variables (gender, age at FD, ISS stage at FD, induction therapy, local radiation pre-/during induction, and remission status postinduction) on PBSC mobilization and collection outcome parameters (prolonged mobilization, plerixafor administration, number of LP sessions, collection goal of $\geq 6 \times 10^6$ $CD34^+$ cells/kg, collection goal of $\geq 4 \times 10^6$ $CD34^+$ cells/kg, overall $CD34^+$ cells collection result), multivariable regression models were calculated. The full model specifications are detailed in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000530056). A stepwise procedure was performed to select relevant and predictive variables. The results are summarized in Table 4 and Figure 1.

Compared to ISS stage I, ISS stage II (OR 1.599 [1.066–2.397]) and III (OR 1.634 [1.096–2.438]) at FD significantly increased the probability of prolonged mobilization. Moreover, compared to lenalidomide-based induction with/without antibodies, VCD/PAD (OR 2.092 [1.383–3.207]), VAD (OR 1.926 [1.049–3.518]), and other induction regimens (group d, OR 3.763 [2.128–6.733]) were significantly associated with prolonged mobilization. The prolongation of mobilization was also found in patients who received local radiation pre-/during induction (OR 2.043 [1.380–3.031]). Gender, age, and remission status postinduction had no significant impact on the duration of mobilization (Table 4; Fig. 1a).

Clinical and treatment variables significantly associated with plerixafor administration during PBSC mobilization and collection were the ISS stage (II compared to I, OR 1.999 [1.05–3.804]), induction therapy (other induction regimens [group d] compared to lenalidomide-based with/without antibodies, OR 4.218 [1.72–10.281]), and local radiation pre-/during induction (OR 2.71 [1.518–4.8]). As VAD induction was administered prior to the approval of plerixafor, it cannot be evaluated regarding plerixafor administration. Gender, age, and remission status postinduction had no statistically significant relevance for plerixafor administration (Table 4; Fig. 1b).

Female gender (OR 1.386 [0.979–1.961]) was associated with prolonged LP (>1 session) to reach the PBSC collection goal with borderline significance. Compared to lenalidomide-based induction with/without antibodies, VCD/PAD induction was associated with reaching the PBSC collection goal in only one LP session. Compared to lenalidomide-based induction with/without antibodies (OR 1.782 [1.022–3.113]) and local radiation pre-/during induction (OR 3.090 [2.091–4.583]), other induction regimens (group d) were significantly correlated with prolonged LP. Age, ISS stage, and remission status postinduction did not have a significant impact on the number of LP sessions (Table 4; Fig. 1c).

Two PBSC collection goal cutoffs were chosen for further evaluation: ≥6 ($n_{\text{reached}} = 587$, $n_{\text{not reached}} = 69$) and ≥4 ($n_{\text{reached}} = 632$, $n_{\text{not reached}} = 24$) $\times 10^6$ $CD34^+$ cells/kg. The probability of failing to reach the PBSC collection goal of $\geq 6 \times 10^6$ $CD34^+$ cells/kg significantly increased with age >60 years (OR 3.824 [2.190–6.968]), ISS stage III compared to stage I (OR 1.87 [1.008–3.468]), and all induction regimens compared to lenalidomide-based with/without antibodies (VCD/PAD OR 2.208 [1.034–5.282] borderline significance, VAD OR 2.613 [0.941–7.381] borderline significance, and other [group d] OR 5.471 [2.220–14.488]) (Table 4; Fig. 1d). Only age >60 years significantly increased the probability of not reaching the PBSC collection goal of $\geq 4 \times 10^6$ $CD34^+$ cells/kg (Table 4; Fig. 1e). The collection goal of $\geq 2 \times 10^6$ $CD34^+$ cells/kg was not addressed, as it was unmet in only 4 patients.

A multivariable linear regression model was calculated to predict the overall collection result. Age >60 years, other induction regimens (group d), and local radiation pre-/during induction reduced the overall collection result by 1.46 (0.34), 1.41 (0.59), and 1.56 (0.41) $\times 10^6$ $CD34^+$ cells/kg, respectively (Table 4).

Discussion

The current study focuses on the identification of clinical and treatment variables associated with the outcome of PBSC mobilization and collection. Beyond

Table 2. Induction therapy and postinduction remission status

Variable	Overall cohort		Induction therapy							
			Lenalidomide-based with/without antibody		VCD/PAD		VAD		Other	
n	790		187		403		102		98	
Induction regimen (including slight modifications) (%)										
VRD	73	(9)	73	(39)						
RVd	23	(3)	23	(12)						
Elotuzumab-VRD	68	(9)	68	(36)						
Isatuximab-RVd	23	(3)	23	(12)						
VCD	312	(39)			312	(77)				
PAD	91	(12)			91	(23)				
VAD	102	(13)					102	(100)		
TAD	36	(5)							36	(37)
Other	18	(2)							18	(18)
≥2 regimens	44	(6)							44	(45)
Number of induction cycles										
Median (range)	4	(2–9)	4	(2–4)	4	(2–7)	3	(2–6)	4	(2–9)
NA (%)	2	(2)	1	(1)	0	(0)	0	(0)	1	(1)
Local radiation pre-/during induction (%)										
Yes	179	(23)	44	(24)	89	(22)	20	(20)	26	(27)
No	611	(77)	143	(76)	314	(78)	82	(80)	72	(73)
Remission status postinduction (%)										
CR	14	(2)	8	(4)	5	(1)	0	(0)	1	(1)
nCR	120	(15)	43	(23)	63	(16)	0	(0)	14	(14)
VGPR	215	(27)	82	(44)	111	(28)	5	(5)	17	(17)
PR	297	(38)	45	(24)	162	(40)	51	(50)	39	(40)
MR	53	(7)	5	(3)	20	(5)	20	(20)	8	(8)
SD	33	(4)	2	(1)	13	(3)	13	(13)	5	(5)
PD	11	(1)	0	(0)	6	(1)	1	(1)	4	(4)
Not applicable	9	(1)	1	(1)	7	(2)	0	(0)	1	(1)
NA	38	(5)	1	(1)	16	(4)	12	(12)	9	(9)

CR, complete response; MR, minimal response; NA, not available; nCR, near complete response; PAD, bortezomib, doxorubicin, dexamethasone; PD, progressive disease; PR, partial response; RVd, lenalidomide, bortezomib, dexamethasone; SD, stable disease; TAD, thalidomide, doxorubicin, dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response; VRD, bortezomib, lenalidomide, dexamethasone.

$CD34^+$ cell collection yield and mobilization failure, further outcome parameters of PBSC mobilization and collection, such as the prolongation of PBSC mobilization, plerixafor administration, number of LP sessions, and different collection goal cutoffs, were evaluated. Additionally, the multiparametric approach evaluating clinical and treatment variables as independent variables contributes to the novelty of the present analysis.

Our analysis indicates that the risk of prolonged mobilization is increased by an advanced ISS stage at FD, VCD/PAD, VAD, and other induction regimens (group d) compared to lenalidomide with/without antibodies and local radiation pre-/during induction. Few previous studies address the parameter of prolonged mobilization (i.e., the duration of G-CSF administration) [19, 27, 28]. These studies assess the prolongation of mobilization as a factor influencing the $CD34^+$ cell collection yield rather than an outcome parameter. Therefore, comparability to our analysis is not given. However, two of these studies associate long intervals between G-CSF administration and PBSC collection with poor mobilization and lower collection results and link prior radiation therapy and the prolongation of mobilization [19, 27].

Variables significantly associated with plerixafor administration are an advanced ISS stage, other induction regimens (group d) compared to lenalidomide-based therapies with/without antibodies, and local radiation pre-/during induction. There is strong evidence that plerixafor can significantly improve and overcome predictors of poor mobilization, and guidelines for

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Table 3. PBSC mobilization and collection

Variable	Overall cohort		Induction therapy							
			Lenalidomide-based with/without antibody		VCD/PAD		VAD		Other	
N	790		187		403		102		98	
Mobilization therapy (%)										
CAD/G-CSF	741	(94)	181	(97)	378	(94)	97	(95)	85	(87)
Other/modifications/G-CSF	43	(5)	4	(2)	24	(6)	4	(4)	11	(11)
G-CSF only	5	(1)	2	(1)	1	(0)	0	(0)	2	(2)
NA	1	(0)	0	(0)	0	(0)	1	(1)	0	(0)
G-CSF dosage (%)										
Filgrastim 5 µg/kg bw/d	615	(78)	125	(67)	362	(90)	55	(54)	73	(74)
Filgrastim 10 µg/kg bw/d	52	(7)	44	(24)	0		0	(0)	8	(8)
Lenograstim 150 µg/m^2/day	69	(9)	18	(10)	22	(5)	19	(19)	10	(10)
Other	1	(0)	0	(0)	1	(0)	0	(0)	0	(0)
NA	53	(7)	0	(0)	18	(4)	28	(27)	7	(7)
Increase in G-CSF dosage during PBSC mobilization (%)										
Yes	299	(38)	49	(26)	158	(39)	39	(38)	53	(54)
No	487	(62)	138	(74)	244	(61)	60	(59)	45	(46)
NA	4	(1)	0	(0)	1	(0)	3	(3)	0	(0)
Plerixafor application during PBSC mobilization and/or collection (%)										
Yes	80	(10)	25	(13)	41	(10)	/	14	(14)	
No	610	(77)	162	(87)	362	(90)	2	(2)	84	(86)
NA	100	(13)	/	/	100	(98)	/			
Prolonged PBSC mobilization										
Delay, median days (range)	0	(0–8)	0	(0–8)	0	(0–3)	0	(0–8)	1	(0–7)
Patients with distinct number of days in delay (%)										
0	489	(62)	140	(75)	244	(61)	60	(59)	45	(46)
1	166	(21)	29	(16)	87	(22)	21	(21)	29	(30)
2	61	(8)	14	(7)	30	(7)	8	(8)	9	(9)
≥3	70	(9)	4	(2)	41	(10)	10	(10)	15	(15)
NA	4	(1)	0	(0)	1	(0)	3	(3)	0	(0)
PB CD34+ cells/µL at the day of first LP session										
Median (range)	8.3	(0.2–38.5)	8.3	(1.2–26)	8.4	(0.2–38.5)	9.5	(0.9–30.6)	5.8	(0.7–27.7)
Mean (SD)	8.7	(4.9)	8.7	(4.9)	8.9	(5.2)	9.9	(6)	6.9	(5.3)
NA	4		1		3		0		0	
LP sessions										
Number of LP sessions, median (range)	1	(1–8)	1	(1–4)	1	(1–4)	1	(1–4)	1,5	(1–8)
Patients with distinct number of LP sessions (%)										
1	530	(67)	118	(63)	287	(71)	76	(75)	49	(50)
2	180	(23)	55	(29)	83	(21)	15	(15)	27	(28)
≥3	80	(10)	14	(7)	33	(8)	11	(11)	22	(22)

Table 3 (continued)

Variable	Overall cohort		Induction therapy							
			Lenalidomide-based with/without antibody		VCD/PAD		VAD		Other	
Overall PBSC collection result CD34+ cells $\times 10^6$/kg										
Mean (SD)	10.3	(4.4)	10.4	(3.7)	10.3	(4.3)	10.9	(5.3)	9.2	(4.9)
Median (range)	9.4	(0.2–38.5)	9.8	(2.4–26)	9.42	(0.2–38.5)	10.3	(1.5–30.6)	8.4	(2.5–32)
Collection goal not reached, $<6 \times 10^6$ $CD34^+$cells/kg (%)	84	(11)	9	(5)	40	(10)	17	(17)	18	(18)
Collection failure, $<2 \times 10^6$ $CD34^+$ cells/kg (%)	4	(1)	0	(0)	2	(0)	2	(2)	0	(0)
NA	6	(1)	2	(0)	4	(1)	0	(0)	0	(0)
Remission status post PBSC mobilization and collection (%)										
CR	19	(2)	10	(5)	5	(1)	0	(0)	4	(4)
nCR	160	(20)	57	(30)	85	(21)	0	(0)	18	(18)
VGPR	204	(26)	66	(35)	114	(28)	7	(7)	17	(17)
PR	252	(32)	36	(19)	131	(33)	50	(49)	35	(36)
MR	32	(4)	2	(1)	15	(4)	11	(11)	4	(4)
SD	37	(5)	2	(1)	14	(3)	11	(11)	10	(10)
PD	33	(4)	4	(2)	15	(4)	10	(10)	4	(4)
Not applicable	9	(1)	0	(0)	8	(2)	1	(1)	0	(0)
NA	44	(6)	10	(5)	16	(4)	12	(12)	6	(6)

CAD, cyclophosphamide, adriamycin, dexamethasone; CR, complete response; G-CSF, granulocyte-colony stimulating factor; LP, leukapheresis; MR, minimal response; NA, not available; nCR, near complete response; PAD, bortezomib, doxorubicin, dexamethasone; PB, peripheral blood; PBSC, peripheral blood stem cells; PD, progressive disease; PR, partial response; SD, standard deviation; SD, stable disease; VAD, vincristine, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response. [a]VAD was given in the pre-plerixafor era.

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Table 4. PBSC mobilization/collection outcome – final model specifications

	Prolonged mobilization (not prolonged vs. prolonged)			Plerixafor administration[a] (no vs. yes)			Number of LP sessions (1 vs. > 1)			Collection goal ≥6 × 10^6 CD34$^+$ cells/kg (reached vs. not reached)			Collection goal ≥4 × 10^6 CD34$^+$ cells/kg (reached vs. not reached)			Overall collection result (×10^6 CD34+ cells/kg)	
Overall *n*[a]	656			459			656			656			656			656	
Subgroup *n*	*n* (not prolonged) = 411 *n* (prolonged) = 245			*n* (no plerixafor) = 391 *n* (yes plerixafor) = 68			*n* (1 LP session) = 441 *n* (>1 LP session) = 215			*n* (reached) = 587 *n* (not reached) = 69			*n* (reached) = 632 *n* (not reached) = 24			Intercept:11.91 (SE 0.371)	
Metrics	OR ($CI_{2.5\%–97.5\%}$)	Estimate (SE)	*p* value	OR ($CI_{2.5\%–97.5\%}$)	Estimate (SE)	*p* value	OR ($CI_{2.5\%–97.5\%}$)	Estimate (SE)	*p* value	OR ($CI_{2.5\%–97.5\%}$)	Estimate (SE)	*p* value	OR ($CI_{2.5\%–97.5\%}$)	Estimate (SE)	*p* value	Estimate (SE)	*p* value
Intercept	0.212 (0.140–0.315)	−1.549 (0.206)	<0.001	0.087 (0.048–0.150)	−2.441 (0.2914)	<0.001	0.388 (0.270–0.553)	−0.946 (0.183)	<0.001	0.018 (0.007–0.039)	−4.043 (0.445)	<0.001	0.014 (0.005–0.031)	−4.266 (0.444)	<0.001	11.46 (0.37)	<0.001
Gender[b] *n* (male, [RC]) = 402 *n* (female) = 254	/			/			1.386 (0.979–1.961)	0.326 (0.177)	0.066	/			/			/	
Age at FD[b] *n* (≤60 years, [RC]) = 354 *n* (>60 years) = 302	/			/			/			3.824 (2.190–6.968)	1.341 (0.294)	<0.001	3.786 (1.560–10.582)	1.331 (0.479)	0.005	−1.46 (0.34)	<0.001
ISS stage at FD[b] *n* (I) = 331; *n* (II) = 158; *n* (III) = 167																	
I versus II	1.599 (1.066–2.397)	0.469 (0.2065)	0.023	1.999 (1.05–3.804)	0.693 (0.327)	0.034	/			1.541 (0.79–2.952)	0.433 (0.333)	0.194	/			/	
I versus III	1.634 (1.096–2.438)	0.491 (0.204)	0.016	1.855 (0.926–3.681)	0.618 (0.350)	0.078	/			1.87 (1.008–3.468)	0.626 (0.314)	0.046	/			/	
Induction therapy[b] *n* (Lenalidomide based with/without antibody) = 175; *n* (VCD/PAD) = 330; *n* (VAD) = 72; *n* (other) = 79																	
Lenalidomide-based with/without antibody versus VCD/PAD	2.092 (1.383–3.207)	0.738 (0.214)	<0.001	0.808 (0.449–1.466)	−0.213 (0.301)	0.479	0.666 (0.445–0.997)	−0.407 (0.205)	0.048	2.208 (1.034–5.282)	0.792 (0.411)	0.054	/			−0.10 (0.41)	0.808
Lenalidomide-based with/without antibody versus VAD	1.926 (1.049–3.518)	0.656 (0.308)	0.033	3.062e−06 (NA–1.065e+36)[c]	−12.696 (609.804)[a]	0.983	0.612 (0.319–1.134)	−0.492 (0.322)	0.127	2.613 (0.941–7.381)	0.961 (0.518)	0.063	/			0.61 (0.61)	0.315
Lenalidomide-based with/without antibody versus other	3.763 (2.128–6.733)	1.325 (0.293)	<0.001	4.218 (1.72–10.281)	1.439 (0.453)	0.002	1.782 (1.022–3.113)	0.578 (0.284)	0.042	5.471 (2.220–14.488)	1.700 (0.473)	<0.001	/			−1.41 (0.59)	0.017
Local radiation pre-/during induction[b] *n* (no, [RC]) = 515 *n* (yes) = 141	2.043 (1.380–3.031)	0.715 (0.200)	<0.001	2.71 (1.518–4.8)	0.997 (0.293)	<0.001	3.090 (2.091–4.583)	1.128 (0.200)	<0.001	/			2.005 (0.791–4.711)	0.696 (0.449)	0.121	−1.56 (0.41)	<0.001
Remission status postinduction[b] *n* (≥VGPR, [RC]) = 318 *n* (<VGPR) = 338	/			/			/			/			/			/	

CI, confidence interval; FD, first diagnosis; ISS, International Staging System; LP, leukapheresis; OR, odds ratio; PAD, bortezomib, doxorubicin, dexamethasone; RC, reference category; SE, standard error; VAD, vincristine, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response; vs, versus. [a]Patients with "NA" in either independent or dependent variables were excluded. Particularly for the dependent variable "Plerixafor administration," the number of "NA" was even higher, as plerixafor was not approved to the time point of PBSC mobilization in a proportion of patients. [b]The distribution of independent variables is not applicable for the plerixafor subgroup. [c]VAD was given in the pre-plerixafor era. Therefore, the VAD induction regimen cannot be addressed in terms of plerixafor administration with high certainty in the statistical analysis.

preemptive (<10 $CD34^+$ cells/μL in peripheral blood before apheresis) and rescue plerixafor administration (<1/3 of the overall collection goal reached during first LP session) are well established [29–31]. Although not considered as an independent variable, our results align with previously published studies: plerixafor is administered in the context of poor mobilization and radiation, and several induction regimens (represented in the other induction subgroup) are known risk factors of poor mobilization [16, 17, 30]. We also associated an advanced ISS stage at FD with plerixafor administration and, therefore, with poor mobilization. This context was not evaluated in previous studies.

Female gender (borderline significance) and local radiation pre-/during induction decreased the probability of reaching the collection goal in one LP session. Moreover, compared to lenalidomide-based induction with/without antibodies, other induction regimens (group d) were also disadvantageous, but VCD/PAD was advantageous in this context. We previously published an analysis indicating an association between radiation therapy before PBSC mobilization and a higher number of LP sessions required to reach the collection goal [19]. The present study aligns with these results and the general evidence on the negative impact of radiation on PBSC mobilization and collection [17]. We identified one corresponding study addressing the number of LP sessions required to reach the collection goal after lenalidomide induction that demonstrated a negative effect of lenalidomide compared to thalidomide/dexamethasone, VAD, or bortezomib-based regimens in a cohort of 61 MM patients [32]. However, VCD/PAD induction therapy was not included as a separate subgroup. Therefore, our data contribute to the body of knowledge, indicating that lenalidomide-based induction is not per se associated with an increased number of LP sessions to reach the collection goal. This finding aligns with somewhat contradictory previous results regarding the adverse effect of lenalidomide on PBSC mobilization [33–35].

Reaching the PBSC collection goal of $\geq 6 \times 10^6$ $CD34^+$ cells/kg was significantly decreased at age >60 years, in patients with an advanced ISS stage, and after all – except lenalidomide-based – induction regimens. Only age >60 years significantly decreased the probability of reaching the PBSC collection goal of $\geq 4 \times 10^6$ $CD34^+$ cells/kg. As crucial for further treatment, mobilization and collection failure is the most addressed parameter, and previous studies focused on a collection result of $< 2 \times 10^6$ $CD34^+$ cells/kg (minimum for one sufficient PBSC graft) [27, 32, 34, 36–44]. In the present study, this collection goal was unmet in only 4 of 790 patients (0.5%). As demonstrated in most previous analyses, age does not seem to be associated with mobilization failure ($< 2 \times 10^6$ $CD34^+$ cells/kg) [37, 43, 45]. However, some studies indicate an adverse effect [41, 44]. The present study indicates that age >60 years is disadvantageous with higher collection goals (4 or 6×10^6 $CD34^+$ cells/kg). We identified two other previous studies that considered the ISS stage; however, it was not associated with mobilization failure [43, 46]. In the present study, ISS stage III was associated with a lower probability of reaching the collection goal of ≥6 but not $\geq 4 \times 10^6$ $CD34^+$ cells/kg. Similar to age, an advanced ISS stage at FD may be relevant only for higher collection goals. The influence of previous lenalidomide treatment remains controversial [5, 39, 47–49]. Our study found no negative impact of lenalidomide on the probability of reaching a specific collection goal. Contrarily, previous lenalidomide treatment was more closely correlated with reaching the $\geq 6 \times 10^6$ $CD34^+$ cells/kg collection goal. Notably, previous radiation therapy was not associated with a lower probability of reaching the ≥6 or $\geq 4 \times 10^6$ $CD34^+$ cells/kg collection goal. In all groups, the LP was performed after induction therapy; therefore, the exposure to lenalidomide with/without monoclonal antibody can be assumed as comparable to other induction regimens in terms of duration. However, a higher G-SCF dosage was administered in approximately one-third of patients receiving lenalidomide-based induction with/without antibodies in the current analysis. This might have overcome the previously described negative impact of lenalidomide on the PBSC mobilization and collection parameters.

In multivariable linear regression, age >60 years, other induction regimens (group d), and local radiation pre-/during induction reduced the collection result by 1.46 (SE 0.34), 1.41 (SE 0.59), and 1.56 (SE 0.41) $\times 10^6$ $CD34^+$ cells/kg, respectively. This evaluation was performed because reaching a predefined collection goal may not be sufficiently sensitive to reveal associations between the parameters. However, the results obtained with the collection goal of $\geq 6 \times 10^6$ $CD34^+$ cells/kg were very similar, indicating the consistency of the statistical analysis. Nonetheless, additional information can be derived for individual patients by estimating an average reduction of the $CD34^+$ cell collection result if one or several risk factors are present.

The present analysis has several methodological strengths. First, the large sample size allows a statistically sufficient multiparametric analysis. Second, assessing multiple PBSC mobilization and collection parameters, beyond the widely established parameters of the "overall collection result" ($CD34^+$ cell yield) and "mobilization failure," engenders a broader picture of PBSC mobilization and collection [17, 27, 29, 31, 41, 43–46, 49–51]. Although a critical parameter, the $CD34^+$ cell yield may not represent an adequate variable for PBSC mobilization and collection assessment. This is due to the

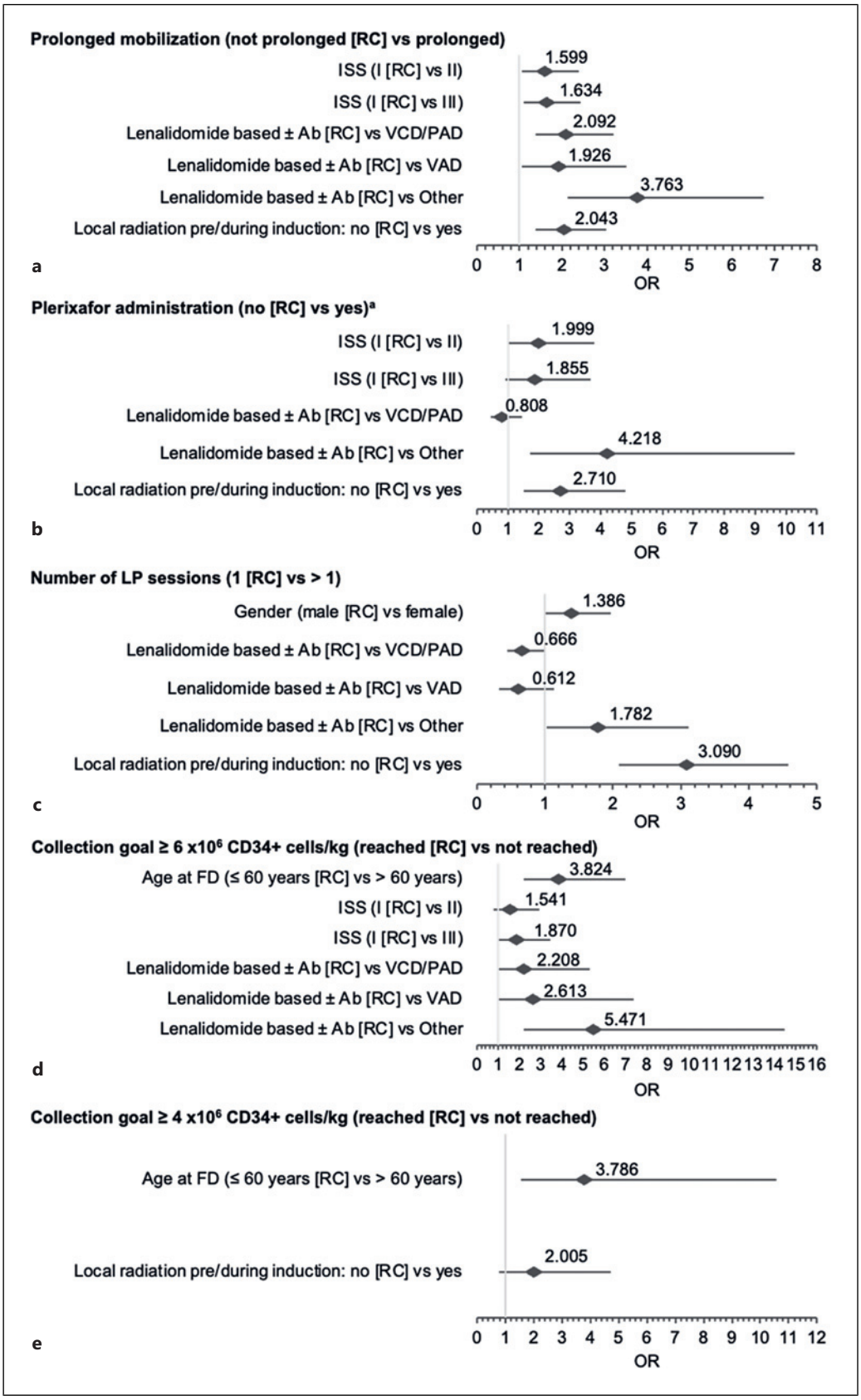

Fig. 1. Prediction of PBSC mobilization/collection outcome – forest plots of final model ORs. The forest plot of final model ORs and the $CI_{2.5\%–97.5\%}$ are given for the analyzed PBSC mobilization/collection outcome parameters (**a–e**). Independent variables contributing to the explanation of the respective PBSC mobilization/collection outcome parameters were included only. For detailed metrics, including *p* values, compare Table 4. [a]Lenalidomide based with/without antibody *n* = 175, VCD/PAD *n* = 252, VAD *n* = 2, and other *n* = 30. There were only 2 patients, who received VAD in the pre-plerixafor era. Therefore, the VAD induction regimen cannot be addressed with high certainty in the statistical analysis and is not shown in the figure. Ab, antibody; CI, confidence interval; FD, first diagnosis; ISS, International Staging System; LP, leukapheresis; OR, odds ratio; PAD, bortezomib, doxorubicin, dexamethasone; RC, reference category; VAD, vincristine, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response; vs, versus.

blood volume processed during an LP session. In specific cases, particularly in good mobilizers in whom a sufficient collection result can be guaranteed, the LP session may be terminated prematurely following a $CD34^+$ cell collection prediction formula, avoiding the risks of LP continuation [52]. In these cases, the $CD34^+$ cell yield does not reflect the full PBSC collection potential. Therefore, collection goal cutoffs and the number of LP sessions required to reach the PBSC collection goal, as evaluated in the present analysis, may be more appropriate. Moreover, focusing on only the PBSC collection result clearly neglects the effort of PBSC mobilization, which may have clinical and economic importance. To reflect PBSC mobilization, the prolongation of mobilization and the need for plerixafor administration were also considered in the present evaluation. Third, the uniform multiparametric evaluation of carefully selected clinical and treatment variables (independent variables: gender, age at FD, ISS stage at FD, induction therapy, local radiation pre-/during induction, remission status postinduction) in the context of PBSC mobilization and collection outcome parameters (dependent variables) allows a direct comparison of the influence of independent variables. To the best of our knowledge, the present analysis is the first broad, standardized, and multiparametric evaluation of PBSC mobilization and collection.

Our study has limitations, one of which is its retrospectivity. However, as well established, PBSC mobilization and collection are usually not a primary research question in current prospective randomized trials, and the vast majority of recently published hypothesis-generating analyses derive their conclusions from retrospective assessments [19, 31, 45, 49]. Furthermore, the subgroup "other induction regimens" (group d) is inhomogeneous and includes not only patients who received different therapies but also those who received ≥2 induction therapies. Therefore, this subgroup should be interpreted with caution. Moreover, VAD induction was administered in the pre-plerixafor era. Therefore, the VAD induction regimen cannot be evaluated regarding the PBSC mobilization outcome parameter "need for plerixafor administration."

Overall, our multiparametric analysis establishes negative associations between female gender, age >60 years, an advanced ISS stage, and local radiation pre-/during induction and PBSC mobilization and collection outcome parameters. The remission status postinduction is not decisive in this regard. Notably, lenalidomide-based induction with/without antibodies generally does not have a negative impact compared to VCD/PAD, VAD, or other evaluated induction regimens. However, it should be considered that a higher G-SCF dosage was administered in approximately one-third of patients receiving lenalidomide-based induction with/without antibodies in the current evaluation. Considering these risk factors in the clinical setting may contribute to optimized PBSC mobilization and collection. Further research efforts should focus on a patient-specific model to predict the respective PBSC mobilization and collection outcome parameters based on individual clinical and treatment variables.

Statement of Ethics

The retrospective data analysis was approved by the Ethic Committee University Hospital Heidelberg (approval number S-102/2009).

Conflict of Interest Statement

Sandra Sauer: travel grants or honoraria for presentations for Celgene, BMS, Janssen, Takeda, and Amgen. Lennart Hieke, Juliane Brandt, and Carsten Müller-Tidow: none. Anita Schmitt: received travel grants from Hexal and Jazz Pharmaceuticals, research grant from Therakos/Mallinckrodt, consultant by Janssen-Cilag and BMS, and is a cofounder of TolerogenixX Ltd. AS is a parttime employee of TolerogenixX Ltd. Joseph Kauer: honoraria Astra Zeneca. Katharina Kriegsmann: advisory board Sanofi; research funding Sanofi, BMS.

Author Contributions

Sandra Sauer, Carsten Müller-Tidow, Anita Schmitt, and Joseph Kauer: conception or design of the work, interpretation of data, critical revision for intellectual content, final approval, and agreement 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. Lennart Hieke: acquisition, analysis, interpretation of data, drafting the work, final approval, and agreement 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. Juliane Brandt: conception or design of the work, critical revision for intellectual content, final approval, and agreement 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. Katharina Kriegsmann: conception or design of the work, analysis, interpretation of data, drafting the work, critical revision for intellectual content, final approval, and agreement 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.

Data Availability Statement

The original data set will be available upon request (including a project plan approved by an ethics committee) and agreement of all authors of the present manuscript given the permission of the Ethic Committee of the University Hospital Heidelberg and a signed/valid Data Transfer Agreement.

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