

# Impact of daratumumab-based induction on stem cell collection parameters in Swedish myeloma patients

Autologous stem cell transplantation (ASCT) is still considered the golden standard of therapy for younger fit patients with newly diagnosed multiple myeloma (NDMM) even in the era of novel induction regimens as it has led to longer progression-free survival in recent trials.<sup>1,2</sup> Recently, two randomized trials evaluated the addition of the anti-CD38 antibody daratumumab to induction and proved that this induces deeper and more durable responses.<sup>3,4</sup> In order to perform ASCT, patient's stem cells need to be collected after a few cycles of induction. Either "steady state" mobilization with cytokines such as filgrastim (G-CSF) or mobilization using chemotherapy such as cyclophosphamide 2-4 g/m<sup>2</sup> followed by G-CSF has been used for this purpose.<sup>5,6</sup> Plerixafor is used as rescue to patients who mobilize poorly after G-CSF or preemptive when high risk for poor mobilization exists.<sup>7,8</sup> A minimum of 2x10<sup>6</sup> CD34+ cells/kg need to be collected prior to and reinfused after high dose melphalan to ensure adequate bone marrow function after ASCT.<sup>5</sup> As a significant portion of myeloma patients can be subjected to tandem ASCT at first line or second ASCT at first relapse the goal often is to collect at least 4x10<sup>6</sup> CD34+ cells/kg. It has previously been reported<sup>9-11</sup> that the addition of daratumumab to induction led to increased use of plerixafor and lower yields of collected CD34+ cells/kg.

In this retrospective study by the Swedish myeloma group, we aimed to report the impact of the addition of daratumumab to induction therapy prior to ASCT on stem cell collection parameters in a real-world population with NDMM.

NDMM patients who proceeded to stem cell mobilization and apheresis at six transplantation centers at different regions in Sweden between February 2020 to November 2021 were included in the study. Upon approval by the Swedish Ethical Committee, local representatives of the Swedish myeloma group retrospectively collected data regarding baseline characteristics, induction regimen, response grade after induction according to the latest IMWG update,<sup>12</sup> mobilization regimen and stem cell collection parameters. Patients with missing apheresis data or switching from a non-daratumumab to a daratumumab-containing induction regimen were excluded. The policy for the use of daratumumab in induction was the same in all the centers as recommended by the Swedish Myeloma Guidelines.

The patients were divided in two groups: daratumumab-treated (patients receiving daratumumab in induction) and non-daratumumab-treated (patients not receiving daratumumab in induction).

The primary outcome was mean CD34+ cells/kg collected by apheresis. Secondary outcomes were the proportion of patients being able to collect >4x10<sup>6</sup> cells/kg, median days of apheresis, the use of plerixafor as rescue to mobilize stem cells and the proportion of patients failing to mobilize stem cells at all.

All the centers had a similar policy regarding stem cell collection method and plerixafor use without changes during the study's observation period. Optia<sup>®</sup> continuous mononuclear collection (CMNC) system was used for apheresis. A standard washout period of 2 weeks from the end of the last induction cycle to the start of the mobilization regimen was applied. Plerixafor was only used as rescue in case of CD34+ cells/mL < 20,000 in the peripheral blood at the day of planned apheresis.

A total of 217 patients were included in the study. Ninety-two (42%) of the patients received daratumumab-containing induction. *Online Supplementary Tables S1 and S2* in the *Online Supplementary Appendix* summarize baseline characteristics as well as induction and mobilization parameters. There were no significant differences between the two groups regarding median age, presence of anemia, hypercalcemia, bone disease at diagnosis as well as bone marrow plasmacytosis, presence of high risk cytogenetics and ISS stage. Equal number of patients in the two groups received radiation during the induction period. The median age was 61 for daratumumab-treated and 63 for non-daratumumab-treated patients. A slightly higher proportion of daratumumab-treated patients had renal failure at diagnosis (21% vs. 10%,  $P=0.052$ ). There was a significantly higher percentage of patients treated with lenalidomide in the non-daratumumab group and thalidomide in the daratumumab group as part of induction. The most common used induction regimen in the non-daratumumab group was VRD (bortezomib, lenalidomide, and dexamethasone) (72% of patients). In the daratumumab group, 53 patients (57%) were treated with D-VTd (bortezomib/thalidomide/dexamethasone) and 34 (37%) with D-VRd. Use of alkylators in induction, mainly cyclophosphamide, was slightly higher in non-daratumumab-treated patients but limited to only a few patients in each group. A higher percentage of daratumumab-treated patients achieved  $\geq$  VGPR at the end of induction (86% vs. 66%,  $P=0.001$ ). Steady-state mobilization was used in 12% of daratumumab treated compared to 3% of non-daratumumab treated patients ( $P=0.015$ ).

The mean value of CD34+ x10<sup>6</sup> cells/kg was significantly lower in patients treated with daratumumab as part of in-

duction,  $5.14 \times 10^6$  cells/kg compared to  $7.22 \times 10^6$  cells/kg in the non-daratumumab-treated population ( $P < 0.001$ , calculated by independent-samples *t*-test). Eighty-six percent of non-daratumumab-treated patients were able to collect  $>4 \times 10^6$  CD34+ cells/kg in comparison to 76% of daratumumab-treated patients ( $P = 0.051$ ) (Figure 1; Table 1). When comparing the impact of different induction regimens in daratumumab-treated patients (D-VRd vs. D-VTd) on the mean value of collected stem cells, no significant difference was observed ( $5.06 \times 10^6$  vs.  $5.14 \times 10^6$  CD34+ cells/kg,  $P = 0.894$ ).

Besides the use of daratumumab in induction, other factors with a statistically significant negative impact on the mean values of collected CD34+ cells in univariate analysis were age  $>60$  years and use of thalidomide or radiation in induction while use of lenalidomide in induction led to a higher mean value of collected CD34+ cells. Sex, alkylator use in induction, number of induction cycles, depth of response at the time of apheresis and use of cyclophosphamide in mobilization had no significant effect on

stem cell yield (Table 2).

Factors with statistically significant impact on the primary outcome in univariate analysis were tested in a multivariate analysis using linear regression. Only the use of daratumumab in induction, age  $>60$  years and radiation during induction proved to significantly affect the study's primary outcome (Table 2).

Five daratumumab-treated patients completely failed to mobilize stem cells compared to just one non-daratumumab-treated patient but this result was not statistically significant ( $P = 0.085$ ). Median days of apheresis were 2 in daratumumab and 1 in non-daratumumab group ( $P = 0.018$ ). There was a significant difference even in mean days of apheresis between the two groups (1.65 days for daratumumab treated vs. 1.42 days for non-daratumumab treated patients,  $P = 0.031$ ). Fourteen daratumumab-treated patients (15%) needed  $>2$  days of apheresis to collect the desired amount of CD34+ cells/kg while only nine (7%) non-daratumumab-treated patients needed  $>2$  days ( $P = 0.074$ ). Plerixafor use as rescue was significantly higher

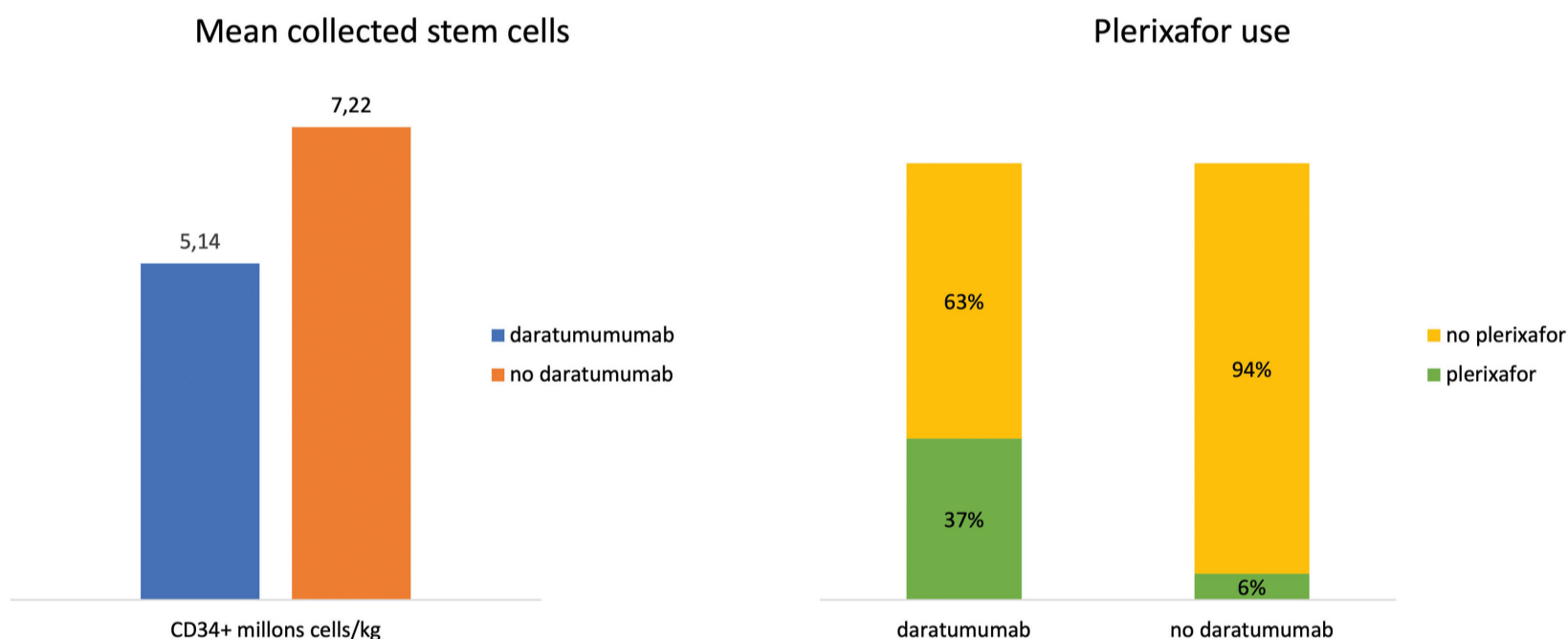


Figure 1. The impact of daratumumab on mean collected stem cells and rescue use of plerixafor.

Table 1. Collected CD34+ stem cells, plerixafor use and days of stem cell collection.

	Daratumumab-treated, N=92 (%)	Non-daratumumab-treated, N=125 (%)	P
Collected CD34+ $\times 10^6$ cells/kg			
Mean	5.14	7.22	$<0.001$
$>4 \times 10^6$	70 (76)	108 (86)	0.051
failure	5 (5)	1 (0.8)	0.085
Plerixafor use	34 (37)	8 (6)	$<0.001$
Days of stem cells collection			
Median	2	1	0.018
Mean	1.65	1.42	0.031
$>2$	14 (15)	9 (7)	0.074

in the daratumumab-treated patients, 37% versus 6% ( $P<0.001$ , Fisher's exact test) (Table 1).

A comparison of the effect of D-VTd versus VTD on the outcome of stem cell mobilization and collection in the randomized phase III CASSIOPEIA study has recently been published.<sup>9</sup> The mean number of collected CD34+  $\times 10^6$  cells/kg was significantly lower ( $6.7 \times 10^6$  vs.  $10 \times 10^6$  cells/kg,  $P<0.0001$ ) and use of plerixafor higher (22% vs. 8%,  $P<0.0001$ ) in the D-VTd arm. Similar results have been reported by Chhabra *et al.*<sup>13</sup> for the GRIFFIN (D-VRd vs. VRd in NDMM with intent to transplant) and MASTER (D-KRd in NDMM) trials as well as in small retrospective series by Manjappa *et al.*<sup>10</sup> and Papaiakevou *et al.*<sup>11</sup>

In the present study we were able to show that the addition of daratumumab to induction leads to statistically significant lower stem cell yield (mean  $5.14 \times 10^6$  vs.  $7.22 \times 10^6$  cells/kg,  $P<0.001$ ), higher mean (1.65 days vs. 1.42 days,  $P=0.031$ ) and median days of apheresis (2 days vs. 1 day,

$P=0.018$ ) as well as increased rescue use of plerixafor (37% vs. 6%,  $P<0.001$ ) in a large, country-wide real-world patient population with NDMM (Figure 1). Daratumumab was the only factor affecting stem cell yield besides age >60 years and radiation during induction in multivariate analysis. Previously identified risk factors for poor stem cell mobilization such as prior therapy with alkylators or lenalidomide were not associated with lower stem cell yield in the present study.<sup>14</sup> The reason for the effect of daratumumab on stem cells collection is unknown but a possible explanation could be a daratumumab-induced deficiency of bone marrow stem cells as these also express CD38 to an extent.

In conclusion, our study confirms in a large real-world population that the addition of daratumumab in induction for NDMM can induce deeper responses but may have a negative effect on stem cell mobilization and collection, leading to lower stem cell yield. As daratumumab-based

**Table 2.** Uni- and multivariate analysis of factors affecting stem cell yield.

	Mean	Univariate analysis	Multivariate analysis	
	CD34+ $\times 10^6$ cells/kg	P	Coefficient B	P
Daratumumab induction				
Yes	5.14	<0.001	-2.099	<0.001
No	7.22		0	
Age >60 years				
Yes	5.87	0.007	-1.535	<0.001
No	7.03		0	
Sex				
Female	6.77	0.134		
Male	6.08			
Induction				
Lenalidomide				
Yes	6.70	0.025	0	0.483
No	5.66		-0.576	
Thalidomide				
Yes	5.51	0.014	-0.928	0.282
No	6.69		0	
Alkylators				
Yes	7.51	0.070		
No	6.23			
Radiation				
Yes	4.66	<0.001	-2.207	<0.001
No	6.64		0	
Cyclophosphamide mobilization				
Yes	6.32	0.796		
No	6.57			
$\geq$ VGPR				
Yes	6.11	0.111		
No	7.09			
>4 induction cycles				
Yes	7.31	0.154		
No	6.30			

VGPR: very good partial response.

quadruplets are rapidly becoming the standard of care in induction, new strategies to facilitate the collection of stem cells should be explored such as omitting cyclophosphamide in mobilization, monitor closely and use early plerixafor in case of low CD34+ cells count in the peripheral blood. This strategy is currently being evaluated in transplantation centers in Sweden.

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### Disclosures

No conflicts of interest to disclose.

### Contributions

KL and MH contributed to the design of the study. All authors contributed to data collection. KL carried out the analysis, compiled the data, and drafted the article. LT, ML, KC, JC, CHB, AIS, SW, SL and MH contributed to the writing of the article. All authors approved the final article.

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### Data-sharing statement

The source data that support our findings are available upon request to the corresponding author.

## LETTER TO THE EDITOR

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