Ulrike Bacher (Orcid ID: 0000-0001-8771-947X)

Michael Nagler (Orcid ID: 0000-0003-4319-2367)

Thomas Pabst (Orcid ID: 0000-0002-6055-5257)

Long-term safety of the stem cell releasing compound plerixafor for peripheral stem cell collection in myeloma patients

Letter to the Editor

Melanie Maechler [1], Ulrike Bacher [2], Michael Daskalakis [2], Henning Nilius [3], Michael Nagler [3], Behrouz Mansouri Taleghani [2], Barbara Jeker [1], and Thomas Pabst[1]

Affiliations: [1] Department of Medical Oncology; [2] Department of Hematology and Central Hematology Laboratory; and [3] University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.

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Corresponding author: Thomas Pabst, MD; Extraordinary Professor; Department of Medical Oncology; University Hospital; 3010 Berne; Switzerland. Phone +41 31 632 0378; E-mail: thomas.pabst@insel.ch

High-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) is the standard consolidation treatment for myeloma patients considered fit for this treatment, and it is associated with better complete remission and survival rates [1,2,3]. A minimum of 2.0×10^6 CD34+ cells/kg b.w. are needed for a single ASCT [4]. For patients with insufficient stem cell mobilization with G-CSF alone, the stem cell releasing compound plerixafor is the rescue compound of choice [4-6]. It triggers additional hematopoietic stem cell release from the bone marrow to the peripheral blood and, thereby, allows a substantial proportion of patients with imminent mobilization failure to collect sufficient stem cells, and it decreases the number of apheresis days [5]. Plerixafor is generally well tolerated, with minor (if at all) drug-related adverse events after administration [7].

However, long-term outcomes of myeloma patients, which received plerixafor, are poorly studied. Consequently, we compared myeloma patients who received at least one dose of plerixafor for peripheral stem cell mobilization to a cohort of myeloma patients not in need of (rescue) plerixafor administration. We specifically investigated whether long-term outcomes were comparable in both groups.

In this single-center study, we included all subsequent patients with multiple myeloma who received HDCT with ASCT at the University Hospital Bern, Switzerland with preceding peripheral stem cell apheresis between 04/2010 and 01/2015, as an intention-to-collect analysis. Induction treatment strategy was consistent at our center with almost all patients receiving VCD (bortezomib, cyclophosphamide, and dexamethasone). We compared all myeloma patients with plerixafor to all myeloma patients without needing plerixafor support in this period.

Myeloma patients received G-CSF and a non-myelosuppressive mobilization chemotherapy with either vinorelbine or, in patients with preexisting neuropathy,

gemcitabine [1,8-10]. In few patients, only G-CSF was used (***Supplementary Table S1***). Plerixafor was administered in poorly mobilizing patients, who failed to achieve a level of 10'000/mL CD34+ cells in the peripheral blood at the day before the planned apheresis procedure. In case of insufficient CD34+ yield on the first collection day, a second day of stem cell apheresis was scheduled.

Primary endpoints of this study were to compare the overall survival (OS) and progression-free survival (PFS) in both patient groups. Details of the statistical analysis including power analysis, and univariate and multivariate Cox proportional-hazard models are provided in the ***Supplementary Information***. We identified 137 patients with multiple myeloma receiving HDCT and ASCT with stem cell apheresis between 04/2010 and 01/2015. Among them, 57 patients received at least one dose of plerixafor during their stem cell mobilization procedure. Concerning clinical characteristics at initial diagnosis, we observed no differences between the two groups. Details of patient and disease characteristics at diagnosis and before mobilization are summarized in ***Supplementary Table S2*.**

We listed details of the mobilization and stem cell collection procedure in ***Supplementary Table S1***. Noteworthy, more patients in the plerixafor group were mobilized with vinorelbine (68.4% vs. 48.8%; p=.02), while less patients with plerixafor received gemcitabine (15.8% vs. 46.3%; p<.01). As we used non-myelosuppressive mobilization regimens, we identified no infectious complications in both groups. Remarkably, the duration of the stem cell collection procedure was shorter in the plerixafor group with a median of 230 minutes compared to 285 minutes in the control group (p<.01).

The number of transplanted CD34+ cells in the plerixafor group tended to be higher with a median of 4.30×10^6/kg compared to the control group with 3.49×10^6/kg

(p=.09). Interestingly, patients treated with plerixafor had a shorter duration of neutropenia than patients without plerixafor (6 days vs. 7 days; p=.03). Also, the duration until neutrophil recovery >0.5 G/l was shorter (median 11 days vs. 12 days; p=.01). Further details regarding high-dose chemotherapy, stem cell transplantation and hematologic recovery are summarized in ***Supplementary Table S3***.

During follow up at 100 days after HDCT as well as at last follow-up, there were no differences in the remission status as depicted in ***Table 1***. The median follow up was comparable in both groups, with 86 months in the plerixafor group and 85 months in the control group (p=.11). Progression occurred in 71.9% of all plerixafor patients and in 73.7% of the control patients (p=.81). The time until first progression was similar in both groups (37 months vs. 34 months; p=.30). Finally, 30 patients in the plerixafor group and 35 patients in the control group have died so far (52.6% vs 43.8%; p=.30). Similarly, the median time from HDCT until death was not different between the two groups (72 months, compared to 58 months for the control group patients; p=.20). In conclusion, we found that progression free and overall survival rates as shown in ***Figure 1*** were similar in both groups (p=.33; and p=.77, respectively).

In the univariate and multivariate analysis only bone marrow infiltration above the median was significantly associated with a decreased progression free survival ***(Supplementary Table S4a).*** The IgG myeloma subtype was the only variable that was significantly associated with better overall survival ***(Supplementary Table S4b)***, whereas plerixafor use had no effect. The theoretical power of the two-tailed t-test ranged from 0.40 for very small effect sizes (Cohens D = 0.3) to 1.00 for large effect sizes (Cohens D = 1.0). For clinically significant effect sizes (Cohens D = 0.5) the calculated power was 0.81. A diagram displaying the power

against the effect size and the case of log-rank test is provided in ***Supplementary Figures S1 and S2***.

Our observations are in accordance with previous reports suggesting that adding plerixafor to G-CSF for stem cell mobilization does not confer a detrimental effect on long-term survival [11,12]. In a phase III study where 167 NHL and 163 MM patients were enrolled and received either plerixafor and G-CSF or placebo and G-CSF, the probability of OS (NHL patients 64% plerixafor versus 56% placebo, MM patients 64% versus 64%) and PFS (NHL patients 50% plerixafor versus 43% placebo, MM patients 17% versus 30%) did not differ between both groups [12].

These data further suggest that plerixafor does not lead to a clinically relevant contamination of the apheresis product with residual myeloma cells. Finally, a recent study suggested no difference of the number of multiple myeloma cells, assessed by flow cytometry, in the peripheral blood and apheresis products between patients with mobilization with G-CSF alone or with additional plerixafor [13]. However, it remains unclear whether CD34+ graft contamination with aberrant plasma cells is associated at all with increased relapse risk in myeloma patients. Consequently, a previous study reported that hematopoietic stem cell purging failed to provide a survival benefit in a phase III trial in myeloma patients [14].

Due to the retrospective character of our study, there may be a number of confounding variables. However, the multivariate analysis including patient age, sex, myeloma subtype, initial stage and bone marrow infiltration failed to identify a significant impact of plerixafor use on OS or PFS. Limitations of our study remain its single-center design, its retrospective character and, inevitably, some heterogeneity of patient characteristics, of induction and mobilization treatments. Nevertheless, we consider our findings relevant since the time of follow up is remarkably long (median follow up

85 months), while plerixafor received EMA approval only 2009. Due to the limited size of both patient groups, the power of the study may not have been sufficient to identify subtle effects, while the power of our study was adequate to detect clinically significant effects. Thus, our study provides additional support to the long-term safety of plerixafor use in myeloma patients. Larger studies with adequately long follow-up may be needed to ultimately clarify our findings.

Conflict of interest: The authors declare no conflict of interest.

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Ethics approval Statement: The study was conducted in accordance with the Declaration of Helsinki. It was approved by a decision of the local ethics committee Bern, Switzerland (decision date 03.11.2009; decision number #236/09). No institutional Review Board approval was needed for this study.

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Table 1. Outcomes.

Parameter	Plerixafor (n=57)	Control (n=80)	Total (n=137)	P-value
Remission status at 100 days after HDCT				
CR	28 (49.1%)	39 (48.7%)	67 (48.9%)	0.97
VGPR	12 (21.0%)	22 (27.5%)	34 (24.8%)	0.39
PR	14 (24.6%)	14 (17.5%)	28 (20.4%)	0.31
SD	0 (0.0%)	0 (0.0%)	0 (0.0%)	
PD	0(0.0%)	3 (3.8%)	3 (2.2%)	0.14
Remission status at last follow-up				
CR	11 (19.3%)	16 (20.0%)	27 (19.7%)	0.92
VGPR	1 (1.8%)	4 (5.0%)	5 (3.6%)	0.32
PR	2 (3.5%)	7 (8.75%)	9 (6.6%)	0.22
SD	1 (1.8%)	5 (6.25%)	6 (4.4%)	0.21
PD	7 (12.3%)	9 (11.25%)	16 (11.7%)	0.85
Unknown	5 (8.8%)	4 (5.0%)	9 (6.6%)	0.38
Median follow-up time, months (range)	86 (11-132)	85 (1-121)	85(1-132)	0.11
Progression	41 (71.9%)	59 (73.75%)	100 (73.0%)	0.81
Median time after HDCT, months (range)	37 (1-110)	34 (2-92)	34 (1-110)	0.30
Death	30 (52.6%)	35 (43.8%)	65 (47.4%)	0.30
Median time after HDCT, months (range)	72 (11-114)	58 (1-118)	61 (1-118)	0.20

HDCT: high-dose chemotherapy; CR= complete remission; VGPR: very good partial remission; PR: partial remission, SD: stable disease; PD: progressive disease.

Figure Legend

Figure 1: (**A**) Progression-free survival and (**B**) overall survival of plerixafor patients (n=57) versus control patients mobilized without plerixafor (n=80).