Plerixafor is effective given either preemptively or as a rescue strategy in poor stem cell mobilizing patients with multiple myeloma

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BACKGROUND: Harvest of more than one CD34+ stem cell transplant has become the standard, to ensure the option for a second autologous transplantation in patients with relapsed or progressive multiple myeloma (MM). Additional administration of the CXCR-4 inhibitor plerixafor has been shown to increase the efficiency of CD34+ stem cell harvest. However, the algorithm when to apply plerixafor is still under debate.

STUDY DESIGN AND METHODS: In this retrospective study, 46 MM patients were categorized into four groups according to their CD34+ stem cell count in peripheral blood (PB) and mobilization with or without plerixafor: Group A comprised poor mobilizers with CD34+ cell counts of fewer than 20 × 10⁶/L in PB. Group B included inadequate mobilizers with CD34+ cell counts of 20 × 10⁶/L or more in PB and a low CD34+ stem cell yield in the first leukapheresis session. Patients receiving plerixafor preemptively (Group A1) and as a rescue strategy (Group B1) were compared to patients continuing stem cell collection with granulocyte–colony-stimulating factor alone (Groups A2 and B2).

RESULTS: In both, the preemptive and the rescue settings, plerixafor enhanced the CD34+ stem cell yield significantly. Poor mobilization and administration of plerixafor was not associated with delayed engraftment.

CONCLUSION: Our data demonstrate that administration of plerixafor is safe and effective and facilitates a significantly higher CD34+ stem cell harvest. Based on the presented data, we propose an algorithm for the use of plerixafor for CD34+ stem cell mobilization and harvesting in poor mobilizing myeloma patients.

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM) is the current standard of care in patients younger than 70 years without serious comorbidities.1,2 Recent clinical studies reported that tandem transplantation may provide a longer disease-free survival than single transplantation in patients with MM. Harvest of two or more adequate stem cell grafts will ensure that the option for a second or third autologous transplantation is retained for patients with relapsed or progressive MM.3,4 A successful ASCT is dependent on a sufficient amount of CD34+ cells for a prompt and durable engraftment. The required number of CD34+ cells for transplantation is still a matter

ABBREVIATIONS: ASCT = autologous stem cell transplantation; BW = body weight; EFS = event-free survival; IM(s) = inadequate mobilizer(s); MM = multiple myeloma; PB = peripheral blood; PBSCs = peripheral blood stem cell(s); PM(s) = poor mobilizer(s).

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Received for publication May 14, 2014; revision received July 4, 2014, and accepted July 8, 2014.

doi: 10.1111/trf.12813

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TRANSFUSION 2015;55:275–283.
of debate; however, most transplant centers regard a minimum of $2 \times 10^8$ CD34+ cells/kg body weight (BW) per transplant as sufficient.\textsuperscript{5}

Mobilized peripheral blood stem cells (PBSCs) have become the main source for ASCT in patients with MM. The use of granulocyte-colony-stimulating factor (G-CSF), alone or in combination with chemotherapy (chemomobilization), is currently the most common strategy applied to collect PBSCs.\textsuperscript{6} PBSC mobilization and collection has been optimized in numerous clinical trials, but a significant proportion of patients failed to mobilize and therefore required a second round of mobilization using salvage regimens.\textsuperscript{7,8} Even salvage regimens showed significant failure in mobilization and are associated with toxicity, morbidity, and increased costs.\textsuperscript{9-11} These patients face some serious consequences such as inability to undergo potential curative transplantation, slow recovery of blood counts after autografting, and higher rate of relapse.\textsuperscript{12-14}

In recent years, some of the underlying physiology of PBSCs has been elucidated, leading to the development of new mobilization strategies. Plerixafor (syn. AMD3100) belongs to a new class of small molecules that reversibly inhibits stromal cell–derived factor-1α binding to its cognate receptor chemokine receptor 4 (CXCR4).\textsuperscript{15,16} Plerixafor has been described as a mobilization agent, mobilizing CD34+ cells and CD34+ stem cell harvest.\textsuperscript{17-20} Although the effect of plerixafor in increasing the CD34+ stem cell yield has been investigated in many studies, the appropriate usage of plerixafor, that is, preemptively or as a rescue strategy, is still under discussion.\textsuperscript{21} Current evidence suggests that the addition of plerixafor is safe and effective in the majority of patients with a low CD34+ stem cell count in PB after mobilization and/or with a poor CD34+ stem cell yield.\textsuperscript{22}

Many studies defined poor mobilizers (PMs) as patients with a CD34+ stem cell count of fewer than $20 \times 10^6$ in PB at maximum stimulation or a collection yield of fewer than $2 \times 10^6$ CD34+ cells/kg BW with a maximum of four apheresis procedures. Approximately 15% of all patients are considered to be PMs.\textsuperscript{2-23} Even for some patients with CD34+ levels of more than $20 \times 10^6/L$ in PB it is difficult to collect an adequate graft for a second transplantation. We defined these patients as inadequate mobilizers (IMs).

We previously demonstrated the efficiency and the economic impact of a rescue stem cell mobilization with plerixafor.\textsuperscript{21} In the present retrospective follow-up analysis we compared the efficiency of plerixafor as a preemptive and rescue strategy in poor and inadequate mobilizing MM patients. On the basis of these findings we developed an algorithm for a rationale use of plerixafor for CD34+ stem cell mobilization.

**MATERIALS AND METHODS**

**Patients**

A group of 46 MM patients mobilizing poor or inadequately were scheduled to receive an ASCT between 2009 and 2012 at the Department of Internal Medicine V at the University Hospital Heidelberg. The patients were categorized into four groups according to their CD34+ stem cell count in PB and mobilization with or without plerixafor. Two groups were considered to be PMs due to a CD34+ cell count below $20 \times 10^6/L$ in PB (Group A1, CD34+ cell counts $<20 \times 10^6/L$ in PB without plerixafor; Group A2, CD34+ cell counts $<20 \times 10^6/L$ in PB with plerixafor). An additional two groups were considered to be IMs with CD34+ cell counts of more than $20 \times 10^6/L$ in PB and comparatively poor yield of collection with first apheresis below one-third of the individual collection goal and/or second apheresis below one-third of the individual collection goal (Group B1, CD34+ cell counts $\geq 20 \times 10^6/L$ in PB with plerixafor; and Group B2, CD34+ cell counts $\geq 20 \times 10^6/L$ in PB without plerixafor). Patients’ age, sex, number of previous therapies, and remission status was evaluated as outlined in Table 1.

**Mobilization methods**

The following chemotherapy regimens were used for mobilization: CAD (1000 mg/m$^2$/day cyclophosphamide on Day 1, 15 mg/m$^2$/day adriamycin on Days 1-4, and 40 mg/day dexamethasone on Days 1-4); Cy (2000 mg/m$^2$/day cyclophosphamide on Days 1 and 2); VCD (1.3 mg/m$^2$/day bortezomib on Days 1, 4, 8, and 11; 900 mg/m$^2$/day cyclophosphamide on Day 1; 40 mg/day dexamethasone on Days 1, 4, 8, 9, 11, and 12); and RD (25 mg/day lenalidomide on Days 1-21; 20 mg/day dexamethasone on Days 1-4, 0-12, and 17-29).

All patients received G-CSF at a dose of 5 to 10 μg/kg BW/day subcutaneously until the end of the stem cell collection period. Patients in Group A1 and Group B1 received additionally plerixafor about 12 hours before the next apheresis procedure due to a poor yield of CD34+ stem cells in the transplant. A median of two injections of plerixafor were administrated to patients of Group A1. In Group B1, patients received a median of one injection of plerixafor.

The clinical goal for 43 patients was to collect three transplants, while for three patients above the age of 70 only two transplants were required (Table 1). Patients’ mobilization regimens were evaluated as outlined in Table 2.

**Transplantation**

The patients underwent high-dose chemotherapy and subsequent transplantation using the collected and
cryopreserved autologous CD34+ stem cells. The minimum number of stem cells for transplantation was $2 \times 10^6$ CD34+ cells/kg BW.

### Clinical data collection

Demographic data, medical histories, laboratory values, and transplant results were extracted from the patients' charts. In addition to white blood cell (WBC) counts and CD34+ stem cell counts in PB, the number of CD34+ cells collected per apheresis, the total CD34+ stem cell yield, and the number of apheresis procedures performed were recorded. The retrospective analysis was approved by the institutional review board and conducted according to the Declaration of Helsinki.

### Statistical analysis

Statistics for quantitative data were described as median with ranges, while categorical data were expressed as a percentage. p values were calculated by t test for quantitative data and by chi-square test for the categorical data. Two-sided p values of less than 0.05 were considered to indicate statistical significance. All calculations and statistical analyses were conducted with computer software (SPSS Statistics 18.0 for Windows, SPSS, Inc., Chicago, IL).

### TABLE 1. Patients’ clinical characteristics

| Parameter                      | CD34+ < 20 × 10^6/L PB | CD34+ ≥ 20 × 10^6/L PB |
|--------------------------------|------------------------|-----------------------|
|                                | Group A1, plerixafor   | Group A2, no plerixafor | Group B1, plerixafor | Group B2, no plerixafor |
| Number of patients             | 11                     | 11                    | 12                    | 12                     |
| Age (years)*                   | 65 (61-73)             | 63 (47-71)            | 61 (40-67)            | 61 (46-72)             |
| Sex (male:female)              | 7:4                    | 7:4                   | 7:5                   | 9:3                    |
| Previous CTx cycles*           | 3 (1-8)                | 4 (3-25)              | 3 (2-7)               | 3 (1-6)                |
| Time from diagnosis to mobilization (months)† | 4 (3-63)             | 6 (3-60)              | 4.5 (3-8)             | 5 (3-114)              |
| Previous irradiation           | 1                      | 2                     | 3                     | 4                      |
| Previous transplantation       | 1                      | 4                     | 1                     | 1                      |
| Remission state at collection  |                        |                       |                       |                        |
| CR                             | 0                      | 1                     | 1                     | 0                      |
| nCR                            | 10                     | 9                     | 8                     | 11                     |
| VGPR                           | 1                      | 1                     | 3                     | 0                      |
| PR                             | 8                      | 5                     | 5                     | 8                      |
| MR                             | 2                      | 2                     | 1                     | 1                      |
| SD                             | 1                      | 1                     | 3                     | 0                      |
| PD                             | 0                      | 0                     | 0                     | 1                      |
| Median CD34+ cells × 10^6/L PB | 9                      | 13                    | 42                    | 42                     |

* Data are reported as median (range).
† Data are reported as number (range).

CR = complete remission; CTx = chemotherapy; MR = minimal response; nCR = near complete remission; NE = not evaluated; PD = progressive disease; PR = partial remission; SD = stable disease; VGPR = very good partial remission.

### TABLE 2. Mobilization regimens in the different groups of patients

| Parameter                          | CD34+ < 20 × 10^6/L PB | CD34+ ≥ 20 × 10^6/L PB |
|------------------------------------|------------------------|-----------------------|
|                                    | Group A1, plerixafor   | Group A2, no plerixafor | Group B1, plerixafor | Group B2, no plerixafor |
| Number of patients                 | 11                     | 11                    | 12                    | 12                     |
| Dose of G-CSF (μg/kg BW)           | 6.3 (3.3-11.5)         | 6.1 (5.0-7.9)         | 6.3 (4.8-11.5)        | 6.4 (4.8-10.4)         |
| Dose of plerixafor (mg/kg BW)      | 0.25 (0.2-0.4)         | 0.29 (0.2-0.4)        | 0.25 (0.2-0.4)        | 0.29 (0.2-0.4)         |
| CAD                                | 9                      | 8                     | 10                    | 7                      |
| CY                                 | 1                      | 1                     | 0                     | 2                      |
| CD                                 | 0                      | 0                     | 1                     | 2                      |
| No preceding CTx                   | 1                      | 0                     | 0                     | 1                      |
| VCD                                | 0                      | 0                     | 1                     | 0                      |
| RD                                 | 0                      | 2                     | 0                     | 0                      |

CAD = cyclophosphamide, adriamycin, dexamethasone; CD = cyclophosphamide, dexamethasone; CTx = chemotherapy; CY = cyclophosphamide; RD = lenalidomide, dexamethasone; VCD = bortezomib, cyclophosphamide, dexamethasone.
RESULTS

Patient characteristics

The demographic features and clinical characteristics of patients mobilized with or without plerixafor are summarized in Table 1. The four groups were not statistically different in age, sex, number of previous therapies, prior radiotherapy, and mobilization regimens.

PB CD34+ stem cell count and plerixafor administration

The CD34+ stem cell count in PB plus blood count was determined as decision guidance for the starting time point of stem cell collection via apheresis. For the PMs the median CD34+ stem cell count in PB at starting time point of apheresis was $11 \times 10^6$ cells/L and for the IMs the median was $42 \times 10^6$ cells/L.

We administered plerixafor in PM and IM patients when the first, second, and/or third apheresis yield was below one transplant (i.e., $<2.0 \times 10^6$ CD34+ cells/kg BW). In the group of PM patients 64% (7/11) started plerixafor in the second apheresis procedure and 36% (4/11) in the third apheresis procedure. Seventeen percent (2/12) of IM patients started plerixafor in the second apheresis procedure, 67% (8/12) in the third apheresis procedure, and 17% (2/12) in the fourth apheresis procedure.

Mobilization harvest

In PM patients, the median (range) harvest of CD34+ cells was $5.6 \times 10^6$ ($2.3 \times 10^6$-$9.4 \times 10^6$) CD34+ cells/kg BW in patients with plerixafor and $3.5 \times 10^6$ ($2.1 \times 10^6$-$9.2 \times 10^6$) CD34+ cells/kg BW in patients without plerixafor ($p = 0.282$). The IM patients in Group B1 harvested significantly more with $8.5 \times 10^6$ ($5.5 \times 10^6$-$16.4 \times 10^6$) CD34+ cells/kg BW in comparison to $4.8 \times 10^6$ ($2.2 \times 10^6$-$10.0 \times 10^6$) CD34+ cells/kg BW in Group B2 ($p = 0.003$). All patients reached a minimum cell yield of at least one-third of the individual collection goal. In Group A1, 64% (7/11) of patients collected two transplants and 36% (4/11) collected three transplants when compared to patients in Group A2 with only 36% (4/11) and 18% (2/11), respectively. In Group B1, 75% (9/12) of patients collected three transplants when compared to 17% (2/12) of patients in Group B2 (Fig. 1C).

Comparison of Group A1 versus Group A2

The median number of CD34+ cells harvested in Group A1 significantly increased from $0.8 \times 10^6$ ($0.2 \times 10^6$-$1.8 \times 10^6$) CD34+ cells/kg BW up to $1.9 \times 10^6$ ($0.7 \times 10^6$-$4.6 \times 10^6$) CD34+ cells/kg BW ($p = 0.0003$) after the administration of plerixafor (Fig. 2A1). In contrast, the number of harvested CD34+ cells per day was not significantly different for Group A2 (Fig. 2A2).

Comparison of Group B1 versus Group B2

The median number of CD34+ cells harvested in Group B1 increased significantly from $1.9 \times 10^6$ ($0.9 \times 10^6$-$2.6 \times 10^6$)/kg BW to $3.7 \times 10^6$ ($2.7 \times 10^6$-$14.1 \times 10^6$)/kg BW ($p = 0.005$) after plerixafor administration (Fig. 2B1). No significant differences between the consecutive harvest days were found for patients in Group B2 (Fig. 2B2). A greater proportion of patients in the plerixafor group achieved two (100% vs. 58%, $p = 0.019$) or even three transplants (75% vs. 17%, $p = 0.006$) when compared to the patients without plerixafor (Fig. 1C).
Transplantation and engraftment

**PMs: patients with (Group A1) or without plerixafor (Group A2)**

In both groups, nine of 11 patients underwent first transplantation after initial mobilization with or without plerixafor. Patients in both groups were transplanted with a median of $2.8 \times 10^6$ CD34+ cells/kg BW. For the patients with plerixafor, the median time of WBC recovery to $1.0 \times 10^9$/L was 16 (11-23) days, whereas the patients without plerixafor needed 14 (10-19) days. This difference was not significant. The median time to platelet (PLT) recovery to an unmaintained level of more than $20 \times 10^9$/L was 11 (10-15) days. Again, this difference was not significant. Three of 11 patients in Group A1 underwent a second transplantation versus one of 11 patients in Group A2. The median number of CD34+ cells for the second transplantation in patients of Group A1 and Group A2 ranged approximately $2.1 \times 10^6$ and $2.7 \times 10^6$/kg BW, respectively. Engraftment of neutrophils and PLTs in both groups was similar (Table 3).

**IMs: patients with (Group B1) or without plerixafor (Group B2)**

All patients with plerixafor underwent transplantation and four of 12 of them underwent tandem transplantation.

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**Table 3. Summary of apheresis yields and transplantation in the different groups of patients**

| Parameter | CD34+ < 20 x 10^6/L PB | CD34+ ≥ 20 x 10^6/L PB |
|-----------|------------------------|------------------------|
|           | Group A1, plerixafor    | Group A2, no plerixafor |
| Yield $\times 10^6$ CD34+ cells/kg BW | 5.6 (2.3-9.4) | 3.5 (2.1-9.2) |
| Number of patients collecting three or more transplants | 4 | 2 |
| Number of patients collecting two or more transplants | 7 | 4 |
| Number of patients collecting one or more transplant | 11 | 11 |
| Patients proceeding to first transplantation | 9 (81.8) | 9 (81.8) |
| Number of CD34+ cells/kg BW | 2.8 (2.1-4.4) | 2.8 (2.1-4.0) |
| Days to WBC count > 1.0 x 10^9/L | 16 (11-23) | 14 (10-19) |
| Days to PLT count > 20 x 10^9/L | 13 (12-16) | 11 (10-15) |
| Patients proceeding to second transplantation | 3.2 (27.3) | 1.9 (91) |
| Number of CD34+ cells/kg BW | 2.1 (2.1-2.7) | 2.7 (-) |
| Days to WBC count > 1.0 x 10^9/L | 14 (12-18) | 14 (-) |
| Days to PLT count > 20 x 10^9/L | 12.5 (11-19) | 10 (-) |

* Data are reported as median (range) or number (%).
comparison, 10 of 12 patients without plerixafor underwent transplantation and no patient proceeded to tandem transplantation. The number of CD34+ cells transplanted, engraftment of neutrophils, and PLTs was analyzed separately and the results for all subgroups are summarized in Table 3.

**DISCUSSION**

Despite major advances in the treatment of myeloma, the disease remains incurable with a median survival of approximately 44 months from the time of diagnosis. ASCT has been considered to constitute the standard approach for first-line therapy of MM patients eligible for transplantation. This has been based on several randomized trials comparing ASCT to conventional chemotherapy. Giralt summarized the data for six of the largest randomized trials comparing single ASCT with conventional alkylator-based chemotherapy. Complete remission rates were significantly higher in the ASCT arms in five of the six trials, the event-free survival (EFS) was superior for ASCT in three of the trials, and two trials showed a survival benefit. A meta-analysis performed on nine randomized trials confirmed that single ASCT was associated with a benefit for the EFS, but not in terms of overall survival. Some studies showed that tandem ASCT significantly improved both EFS and overall survival. The benefit was mostly restricted to those not achieving a very good partial remission with the first ASCT. Therefore, a CD34+ stem cell harvest of more than two transplants should be collected before first ASCT. The addition of plerixafor to G-CSF as first-line regimen for PBSC mobilization has been shown to be safe and effective in several Phase III randomized studies in MM and NHL patients undergoing ASCT as well as in multiple Phase II and retrospective studies in difficult-to-mobilize patients. Plerixafor was already administered before the first apheresis procedure in these studies. However, the optimal timing of plerixafor administration is still under debate. Currently an EBMT group of experts published a position paper on this subject. So far most studies focused on the prediction of PMs and on the administration of plerixafor according to the CD34+ stem cell count in PB. Rosenbaum and colleagues has validated a formula on the basis of the CD34+ stem cell count in the PB and the processed blood volume to predict the CD34+ stem cell yield thereupon to make a rationale decision on the use of plerixafor. However, the absence of a uniformly accepted algorithm

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**Fig. 3. Recommendation of plerixafor administration in the course of CD34+ stem cell mobilization in MM patients.** After chemomobilization of MM patients measurement of CD34+ stem cells in PB is performed to identify poor and borderline PMs. In case of fewer than 10 × 10^6 CD34+ cells/L PB administration of plerixafor is recommended in accordance with EBMT guidelines. Borderline PMs should be subjected to an evaluation leukapheresis procedure if the individual collection goal is not more than two transplants. The second decision-making step depends on the result of the first leukapheresis procedure. If less than one-third of the individual collection goal can be reached, the administration of plerixafor is recommended. This decision-making process is continued until a sufficient stem cell number has been reached.
predicting a mobilization failure and internationally differing costs for the use of plerixafor and apheresis procedures have led to institute-specific algorithms for mobilization.

In our study we examined the efficiency of plerixafor for mobilization and stem cell harvest of at least two and more transplants after the first, second, or third apheresis procedure in poor and inadequately mobilizing MM patients and developed consequently an algorithm for the rationale timing of plerixafor.

We found a significant increase in the median number of CD34+ stem cells harvested after the administration of plerixafor (p ≤ 0.005). All patients reached one transplant. However, a significantly higher proportion of all patients receiving plerixafor achieved at least two (83% vs. 48%) or even three transplants (57% vs. 17%) than patients without plerixafor. Moreover, plerixafor could even rescue the CD34+ stem cell harvest again when it subsided under G-CSF mobilization by the second and/or third apheresis procedure.

Based on the observation that patients in the PM group with a CD34+ cell count in between 11 × 10^6 and 19 × 10^6 cells/L defined as borderline PMs collected a median below 1.5 × 10^6 CD34+ stem cells/kg BW and needed at least two apheresis procedures to reach one transplant, we developed an algorithm indicating the administration of plerixafor at an early stage in PM patients to increase the chance for the collection of two to three transplants (Fig. 3).

Furthermore, according to our engraftment data poor mobilization and the administration of plerixafor for stem cell mobilization was not associated with delayed engraftment as long as 2.0 × 10^6 of CD34+ cells/kg BW could be harvested and transplanted. Furthermore, more patients in the group with plerixafor had a chance to proceed to a second transplantation.

In summary, administration of plerixafor in the preemptive and rescue setting is safe and effective and results in a higher probability to achieve the CD34+ stem cell yield for a second transplantation in MM patients. According to our data, the administration of plerixafor should be considered at an early stage in PM patients. For IM patients, the administration of plerixafor can start at a later stage. We propose a treatment algorithm as summarized in Fig. 3. Further studies will help to validate this recommendation in the clinical setting of CD34+ stem cell mobilization in patients.

CONFLICT OF INTEREST
The first author and all co-authors have no potential conflicts of interest to disclose, except the following: PW—received honorarium for lectures from Sanofi and consulting fee or honorarium from ETICHO; MH—received speaker’s fee from Celgene and grants for scientific research from Celgene and Genzyme; ADH—consultancy, honoraria, and membership on Advisory Boards of Genzyme/Sanofi-Aventis; AS—received a research grant from Sanofi.

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