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# Mobilization Strategies in Myeloma Patients Intended for Autologous Hematopoietic Cell Transplantation

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**Keywords**

Mobilization of blood grafts · CD34$^+$ cells · Multiple myeloma · Granulocyte colony-stimulating factor · Plerixafor · Graft composition

**Abstract**

***Background:*** Multiple myeloma is currently the leading indication for autologous hematopoietic cell transplantation (AHCT). A prerequisite for AHCT is mobilization and collection of adequate blood graft to support high-dose therapy. Current mobilization strategies include granulocyte colony-stimulating factor (G-CSF) alone or in combination with chemotherapy most commonly cyclophosphamide (CY). More recently, plerixafor has become into agenda especially in patients who mobilize poorly. In the selection of a mobilization method, several factors should be considered. ***Summary:*** Preplanned collection target is important as G-CSF plus plerixafor is more effective in the mobilization of CD34$^+$ cells than G-CSF alone. On the other hand, CY plus G-CSF is superior to G-CSF only mobilization. Previous therapy and age of the patients are important considerations as G-CSF alone may not be effective enough in patients with risk factors for poor mobilization. These factors include extensive lenalidomide exposure, irradiation to bone marrow-bearing sites, higher age, or a previous mobilization failure. Also, local preferences and experiences as well as the number of apheresis needed are important issues as well as cost-effectiveness considerations. Mobilization method used may have implication for cellular composition of collected grafts, which might have an impact on posttransplant events such as hematologic and immune recovery in addition to also potential long-term outcomes. ***Key Message:*** Currently, G-CSF alone and preemptive plerixafor if needed might be considered as a standard mobilization strategy in MM patients intended for AHCT.



## Introduction

Multiple myeloma (MM) is currently the leading indication for autologous hematopoietic cell transplantation (AHCT) in both Europe and worldwide. According to the most recent report of European Society for Blood and Marrow Transplantation (EBMT) registry in 2020, more than 13,000 autotransplants were reported to be performed in MM patients [1]. Practically, all transplants were performed with the support of mobilized blood grafts.

MM has been a standard indication for AHCT for more than two decades based on several randomized studies [2, 3]. There has been a real revolution in the management of MM starting with immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), more recently

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antibodies (daratumumab, elotuzumab, isatuximab), and bispecific antibodies (teclistamab, elranatamab, talquetamab), and CAR-T constructs (idecabtagene vicleucel, ciltacabtagene autoleucel). High-dose melphalan followed by autologous graft infusion has retained its important role also in the era of novel agents. Currently, AHCT is the backbone, where novel drugs are incorporated in an increasing proportion of MM patients currently considered as transplant-eligible.

Early randomized transplantation studies in MM patients were performed in patients younger than 65 years of age [4, 5]. Subsequently, along with increasing experience, the upper age limit for AHCT has risen to about 70 years. Also selected MM patients over 70 years of age might be considered transplant-eligible [6–8].

Although majority of MM patients receive only a single AHCT, tandem transplants are still used in some centers especially for high-risk patients although a definitive benefit of this approach is unclear with current treatment schemes. On the other hand, second transplant in the treatment of later relapse or progression has gained some popularity [9–12]. Consequently, the International Myeloma Working Group together with the Blood and Marrow Transplant Clinical Trials Network, the American Society of Blood and Marrow Transplantation, and the European Society of Blood and Marrow Transplantation recommended a salvage AHCT in transplant-eligible patients who relapse or progress >18 months from the initial transplant [13]. In the era of commonly used maintenance therapy posttransplant, a more recent paper of an expert panel recommended a second AHCT after response of at least 36 months after the first AHCT [14].

## Impact of Induction Therapy on Mobilization Efficiency

Response to induction therapy before mobilization is an important issue regarding effective mobilization. At least partial response or if possible very good partial response is important to ensure good mobilization of progenitor cells. Corticosteroids, mostly dexamethasone, are used in all induction combinations in MM and do not apparently have any adverse effects regarding mobilization of $CD34^+$ cells. Cyclophosphamide (CY) is included in some induction therapies with, e.g., bortezomib and dexamethasone (VCd). CY appears not to hamper the mobilization of blood grafts either and has successfully been used for the mobilization of blood grafts for almost three decades [15].

*Proteasome Inhibitors*

*Bortezomib* has clearly the longest history of proteasome inhibitors in MM. In the FMG-MM01 study of the Finnish Myeloma Group, bortezomib combined with dexamethasone (Vd) was an effective therapy in newly diagnosed MM. The median number of $CD34^+$ cells collected after mobilization with low-dose (LD) CY (2 g/$m^2$) plus G-CSF after four Vd induction cycles was as high as $9.9 \times 10^6$/kg [16]. More recently, bortezomib-dexamethasone has been combined with thalidomide (VTd) [17, 18] or lenalidomide (VRd) [19–21].

*Carfilzomib* has usually been used in a relapse setting but has also been evaluated in clinical studies as an induction therapy. In a study combining four cycles of carfilzomib with lenalidomide and dexamethasone (KRd) in transplant-eligible patients, the median number of $CD34^+$ cells collected was $8.2 \times 10^6$/kg after G-CSF plus plerixafor (PLER) mobilization [22]. In a nonrandomized comparison, KRd-treated patients achieved a bit lower number $CD34^+$ cells collected compared to VRd-treated patients and about 5% of the patients failed to reach the minimal collection target of $2 \times 10^6$/kg $CD34^+$ cells [23].

*Ixazomib* is not approved for newly diagnosed MM patients, and there are currently limited data on its effect in the mobilization of $CD34^+$ cells. Mobilization with G-CSF with or without PLER after a median of four cycles of ixazomib, lenalidomide, and dexamethasone (IRd) resulted in a median collection of $11.6 \times 10^6$/kg $CD34^+$ cells [24]. A phase 2 NMSG#23/15 study including four cycles of IRd induction followed by AHCT and maintenance is ongoing in Nordic and Baltic countries (NCT03376672). The majority of the 108 patients received CY + G-CSF as a mobilization therapy and PLER was used in 25% of the patients resulting in a median number of $6.3 \times 10^6$/kg $CD34^+$ cells collected [25].

*Immunomodulatory Drugs*

*Thalidomide* has been used for the treatment of MM for two decades, initially as salvage treatment in heavily pretreated patients and later as induction therapy with dexamethasone or more recently in triplets like VTd [17, 18]. Although thalidomide has some negative impact in the mobilization of $CD34^+$ cells [26], this appears not to have a major clinical significance. An exception is perhaps the use of thalidomide combined with cyclophosphamide and dexamethasone (CTd), where significant problems in the mobilization of blood grafts have been reported [27].

*Lenalidomide* has been used for the treatment of relapsed or refractory MM for more than a decade. More recently, lenalidomide has been extensively used also as a part of induction therapy combined with dexamethasone +/− bortezomib in both transplant-eligible and nontransplant-eligible patients. Prolonged lenalidomide exposure has been associated with a significant risk of collection failure especially when G-CSF alone mobilization is used [28, 29]. Use of G-CSF with PLER appears to result in adequate mobilization in the

lenalidomide-exposed patients [30]. Another possibility is to use CY plus G-CSF [26] for mobilization purposes in these patients. VRd triplet appears to be associated with a significant risk of collection failure (8.7%) with a G-CSF alone mobilization [19]. In a more recent phase 2 study, mobilization with CY 3 g/m$^2$ plus G-CSF after three VRd cycles resulted in successful collections in all but 1/31 patients, although five patients needed a second mobilization attempt to reach the collection target of 5 × 10$^6$/kg of CD34$^+$ cells [20]. In the Finnish randomized phase 2 mobilization study (FMG-MM02) (G-CSF alone or with CY 2 g/m$^2$) in MM patients treated with three VRd cycles (lenalidomide 14 days/cycle), all patients achieved the minimal collection target (>2 × 10$^6$/kg CD34$^+$ cells) with limited need for PLER [31]. In another study in patients mobilized with CY 2 g/m$^2$ + G-CSF, the impact of limited lenalidomide exposure (median three cycles) was modest, but more apheresis sessions (2 vs. 1) were needed to reach the minimum graft (>2 × 10$^6$/kg CD34$^+$ cells) in the lenalidomide-exposed patients [32]. In a Spanish trial, the patients were mobilized after three VRd cycles, and the majority received G-CSF only mobilization and PLER was used in 12% of the patients. The median number of CD34$^+$ cells collected was 4.66 × 10$^6$/kg [33]. A French single-center analysis observed that VRd-treated patients needed more often PLER and more apheresis sessions compared to VTd [34]. To conclude, in transplant-eligible patients with lenalidomide exposure, mobilization and collection should be considered after three or four cycles and PLER might be added preemptively to G-CSF if needed. Another possibility is to use LD CY plus G-CSF.

*Antibodies*

Currently, two CD38 antibodies daratumumab and isatuximab and a SLAMF7 antibody elotuzumab have been approved for the treatment of relapsed MM. In a Cassiopeia trial (NCT02541383), daratumumab + VTd was compared to VTd as an induction therapy and showed a significant difference in the total number of CD34$^+$ cells collected after CY + G-CSF mobilization (6.7 × 10$^6$/kg vs. 10.0 × 10$^6$/kg), respectively [35]. A real-world study from Sweden showed that adding daratumumab to induction therapy led to significantly lower CD34$^+$ cell yields (5.1 vs. 7.2 × 10$^6$/kg), more apheresis days, and more common use of PLER [36]. A recent retrospective analysis of MASTER and GRIFFIN trials suggested that four cycles of daratumumab- and lenalidomide-based quadruplets had a minimal impact on mobilization capacity of CD34$^+$ cells [37]. The cause for probably lower stem cell yields after daratumumab exposure is not known, but CD38 is expressed also on CD34$^+$ hematopoietic progenitor cells and is supposed to have some interference on stem cell mobilization [35].

## How Much to Collect?

Blood graft contains many cell types in addition to neutrophils, red cells, and platelets. The main function of the blood graft is to restore hematopoiesis and immune system after high-dose therapy. The main functions of the various cell types of the grafts are depicted in Table 1. In clinical practice only the amount of CD34$^+$ cells is routinely measured from the collection bags after apheresis with flow cytometry. Quality-assurance systems require validation of processes including measurement of CD34$^+$ counts after processing and freezing, but this is not a routine in all transplant centers.

*CD34$^+$ Cell Dose*

A significant proportion of CD34$^+$ cells are lost or are not viable after processing, freezing, and thawing [39, 40]. Our own experience suggests a median loss of 34% CD34$^+$ cells as assessed with 7-AAD for viability [40, 41]. The minimal collection target has been at least 2 × 10$^6$/kg CD34$^+$ cells for more than two decades. As there are so far no prospective randomized studies evaluating optimal CD34$^+$ cell dose to be collected and infused after high-dose therapy, there is a continuous debate on the topic.

The number of CD34$^+$ cells infused is associated with the tempo of platelet recovery after high-dose therapy [39, 42, 43]. The impact of CD34$^+$ cell dose on posttransplant neutrophil recovery, however, seems to be negligible [39, 40, 43, 44]. More recently, a very low graft CD34$^+$ cell counts (<1.0 × 10$^6$/kg) measured after cryopreservation in myeloma patients have been shown to lead to significantly delayed platelet engraftment with no clinically relevant thrombocytopenia in the long term [40].

In 2009, the International Myeloma Working Group suggested a collection of at least 4 × 10$^6$/kg CD34$^+$ cells for a single transplant and 8–10 × 10$^6$/kg if feasible to allow two transplants [45]. Although at present there appears to be no important role for tandem transplants, an option for a second transplantation should be considered especially in patients <65–70 years of age. An extra collection, which might be needed in a significant percentage of the patients, is feasible and is apparently associated with less efforts and costs compared to re-mobilization after a single high-dose therapy [46].

There are conflicting data regarding effect of CD34$^+$ cell dose for long-term outcome of MM patients after AHCT. Some retrospective studies suggest superior progression-free survival (PFS) [47] or even overall survival (OS) [47, 48] in patients receiving higher CD34$^+$ cell doses, whereas some studies have not found such a relationship [49, 50]. There are studies suggesting that poor mobilization may be in fact associated with shortened PFS and OS [51]. An Italian phase 3 study observed that poor mobilizers (<4 × 10$^6$/kg CD34$^+$ cells collected) had shorter PFS as well as OS compared to the patients mobilizing better [52]. Our

**Table 1.** Potential importance of blood graft characteristics in autologous hematopoietic cell transplantation [38]

| Cell type | Potential importance |
|---|---|
| $CD34^+$ cells | Hematologic recovery, outcome |
| $CD34^+CD133^+CD38^-$ cells | Early hematologic recovery, outcome |
| Lymphocyte subsets (mostly T) | Immune recovery, outcome |
| NK cells | Immune recovery, outcome |
| DCs | Immune recovery, outcome |
| Tumor cells | Outcome |

NK, natural killer; DC, dendritic cells.

recent analysis of MM patients included in the prospective GOA study showed that also patients receiving very low amount of cryopreserved viable $CD34^+$ cells ($<1 \times 10^6$/kg) had comparable outcome compared to patients receiving higher amount of $CD34^+$ cells [40]. To conclude, although not defined adequately in prospective studies, collection of at least 3–4 $\times$ $10^6$/kg $CD34^+$ cells for a single transplant and 6–8 $\times$ $10^6$/kg if a rescue transplantation could be considered [45] in order to shorten especially the duration of thrombocytopenia after AHCT.

*Other Cells*

Blood grafts contain many other cell types than $CD34^+$ cells, e.g., $CD34^+CD133^+CD38^-$ cells (about 5% of $CD34^+$ cells) and a lot of various lymphocytes (20–30 times more than $CD34^+$ cells, typically 150–250 $\times$ $10^6$/kg), whose amount is influenced by the mobilizing method used [41, 53]. These include $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells, much less natural killer cells (about the same amount as $CD34^+$ cells), and even less CD19-positive B lymphocytes [43]. Limited data are available on the importance of these cell types in regard to posttransplant recovery and outcome, and these cell types are not usually measured outside specific clinical studies.

The amount of $CD34^+CD38^-$ hematopoietic cells may be important for early hematopoietic engraftment [54, 55]. In the GOA study, we observed that a higher amount of $CD34^+CD133^+CD38^-$ cells ($>0.065 \times 10^6$/kg) was associated with better PFS in a multivariate model without impact in OS [43]. The only graft component that seemed to associate with better OS in a multivariate analysis was the amount of $CD3^+$ lymphocytes with a cutoff point of $>20 \times 10^6$/kg [42]. In some previous studies, a higher lymphocyte dose with clearly higher cutoffs has been associated with better posttransplant outcome potentially explained by a more rapid immune recovery associated with a higher graft lymphocyte dose [56, 57]. In a recent multicenter retrospective study, the G-CSF mobilization was associated with longer time to next treatment as well as better OS compared to CY + G-CSF mobilization possible due to better immune recovery posttransplant [58]. Clearly, more data are needed regarding potential prognostic value of immune cells in the grafts as well as importance of immune recovery for long-term myeloma control and outcome.

## Current Mobilization Methods

*Chemotherapy plus G-CSF (Chemomobilization)*

Historically, chemotherapy, especially CY plus granulocyte colony-stimulating factor (G-CSF), has been used widely for the mobilization of blood grafts for transplant purposes (Table 2). CY has been used in variable doses ranging from 1.5 g/m$^2$ up to 7 g/m$^2$. A French retrospective study [59] evaluated CY 4 g/m$^2$ vs. CY 7 g/m$^2$ and concluded that 4 g/m$^2$ dose had less hematologic as well as nonhematologic toxicity. We compared retrospectively CY 2 g/m$^2$ versus CY 4 g/m$^2$ and found these equally effective after induction with vincristine, doxorubicin, and dexamethasone, but the lower dose was less toxic and more practical [60]. There has been still ongoing discussion on the optimal CY dose [61]. As there appears to be no effect on long-term outcome when CY is used for mobilization of blood grafts [62–64], the only justification to use CY with G-CSF is that it appears to be more effective in terms of mobilizing $CD34^+$ cells than G-CSF alone mobilization, especially that deals with higher CY doses [65]. We feel safe to use CY 2 g/m$^2$ if chemotherapy is considered necessary in MM patients who received induction with novel agents including lenalidomide [31]. Higher CY doses are clearly more toxic and need more supportive care with associated costs. The dose of filgrastim has been usually 5 μg/kg if added to CY. In addition to filgrastim, also off-label use of pegfilgrastim after CY has been reported in MM patients [66]. In addition to CY, also CY combined with etoposide [67], intermediate-dose cytarabine [68], and vinorelbine [69] and combinations like CAD (cyclophosphamide, doxorubicin, dexamethasone) [70] and DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) [71] have been used for mobilization purposes in MM patients.

*G-CSF Alone (Cytokine Mobilization)*

In the early days of blood graft mobilization, either nonglycosylated filgrastim or glycosylated lenograstim was mostly used [72]. Biosimilar filgrastim appears to be comparable to original filgrastim and has the advantage of lower costs [73, 74]. The dose of filgrastim when used alone for mobilization purposes has been 10 μg/kg/day and usually four doses are given before the first evaluation of blood $CD34^+$ counts in order to consider the start of

**Table 2.** Pros and cons of various mobilization methods

| Pros | Cons |
|---|---|
| Chemotherapy + G-CSF | |
| Sufficient collection in 1 session in most patients (depending on collection targets) | Need for hospitalization (depending on the regimen used)<br>Potential need for transfusions<br>Potential impact on the quality of life |
| More $CD34^+$ cells | Less lymphocytes<br>Do not improve the control of MM or outcome |
| G-CSF alone | |
| Easy outpatient procedure | May need more aphereses |
| Cheaper (depending on the need of PLER) | More need for PLER use |
| PLER | |
| Improves $CD34^+$ cell yield<br>Improves lymphocyte yield | Expensive[a] |

[a]Unless generic preparation is available.

apheresis. More recently, pegylated filgrastim (pegfilgrastim) has also been used for mobilization purposes [75, 76], although mobilization of blood grafts is not an official indication for this drug. A recent study has also evaluated the use of another long-acting G-CSF lipegfilgrastim for mobilization purposes in MM patients [77].

*Plerixafor*

PLER is a selective and reversible chemokine receptor CXCR4 antagonist that enhances stem cell mobilization by blocking the interaction between CXCR4 and CXCL12 [78]. PLER is administered as a subcutaneous injection(s) and reaches peak levels 30 min after a single injection. PLER is mainly eliminated by the kidneys and its dosage should thus be reduced in patients with renal failure.

Based on data from phase 3 trials [79, 80], PLER was approved by the US FDA in December 2008 for use in patients with NHL and MM, to mobilize hematopoietic stem cells for autologous use. According to the EMA decision in July 2009, PLER is indicated in combination with G-CSF to enhance the mobilization of hematopoietic stem cells for collection and subsequent autologous transplantation in adult patients with lymphoma and myeloma with poor $CD34^+$ cell mobilization. Phase 3 trials were based on mobilization with G-CSF alone, but other studies have confirmed that PLER can be used safely in addition to G-CSF with or without chemotherapy, resulting in the mobilization of significantly more $CD34^+$ stem cells compared with traditional approaches, even in patients with a prior mobilization failure [81–83].

There are three main strategies for PLER use in clinical practice: PLER can be given to all patients predicted to have poor mobilization ("up-front setting") [79], given only if it becomes apparent that stem cell mobilization will be inadequate ("preemptive setting") [84, 85], or given in patients with a prior mobilization failure [81]. The up-front strategy has the problem that it may be hard to identify in advance poorly mobilizing patients with need for PLER, leading to some wrongly predicted patients receiving PLER unnecessarily. The up-front setting is thus unlikely to be either the most cost-effective or the most clinically effective approach [84]. However, some studies have shown that the up-front use of PLER with G-CSF was highly efficient and cost-effective compared to mobilization with CY + G-CSF [86, 87]. The preemptive use of PLER has gained increasing attention and is currently the recommended strategy for PLER use [84, 88]. Various guidelines and algorithms have been published for triggering the initiation of PLER in a preemptive setting based mainly on blood counts and the number of $CD34^+$ cells in the peripheral blood on the morning of apheresis. The phase of mobilization is commonly considered, as well as possible yields of prior collections. With steady-state mobilization (G-CSF alone), aphereses are usually initiated after four days of G-CSF, and PLER is usually indicated if the blood $CD34^+$ cell count (B-$CD34^+$) is $<10 \times 10^6$/L on day + 4 or day + 5 after the initiation of G-CSF [89]. The UK consensus statement suggests that the trigger for preemptive PLER should be a B-$CD34^+$ count $<15–20 \times 10^6$/L, and preemptive PLER is also recommended if the day 1 apheresis yield is $< 1 \times 10^6$ $CD34^+$ cells/kg [84]. However, the situation is more complex in patients mobilized with chemotherapy and G-CSF, to whom there are no generally accepted thresholds to guide the initiation of preemptive PLER. We previously published an algorithm for preemptive PLER use after chemomobilization (CY 2 or 4 g/$m^2$ + G-CSF) by combining a rising WBC count of $>5–10 \times 10^9$/L with a B-$CD34^+$ cell count $<10 \times 10^6$/L [90]. Several other algorithms have also been published in relation to this setting [91, 92]. The EBMT consensus statement suggested that

**Table 3.** Effect of mobilization regimen on autologous graft content in myeloma patients

| Parameter | G-CSF | CT + G-CSF | PLER use | Reference |
|---|---|---|---|---|
| $CD34^+$ | + | ++ | | Gertz et al. 2009 [65] |
| | + | | ++ | Dipersio et al. 2009 [79] |
| | + | + | ++ | Worel et al. 2017 [53] |
| | + | ++ | | Turunen et al. 2021 [43] |
| $CD34^+CD133^+CD38^-$ | + | ++ | | Turunen et al. 2021 [43] |
| | + | | +++ | Fruehauf et al. 2009 [96] |
| $CD3^+$ | ++ | + | | Hiwase et al. 2008 [57] |
| | ++ | + | | Skerget et al. 2016 [93] |
| | ++ | + | +++ | Turunen et al. 2021 [43] |
| | ++ | + | | Rees et al. 2022 [95] |
| $CD3^+CD4^+$ | ++ | + | ++ | Turunen et al. 2021 [43] |
| $CD3^+CD8^+$ | ++ | + | ++ | Turunen et al. 2021 [43] |
| NK cells | ++ | + | | Skerget et al. 2016 [93] |
| | ++ | + | +++ | Turunen et al. 2021 [43] |
| $CD19^+$ | + | + | ++ | Turunen et al. 2021 [43] |

NK, natural killer; PLER, plerixafor.

PLER should be used in patients with a B-$CD34^+$ count <10 × $10^6$/L prior to apheresis, while a dynamic approach based on the patient's disease characteristics and prior treatment should be employed in patients with a B-$CD34^+$ count of 10–20 × $10^6$/L. These suggestions should be considered when collecting the minimum number of $CD34^+$ cells (>2 × $10^6$ $CD34^+$ cells/kg) for AHCT [89].

*Mobilization Method and Graft Content*

Mobilization method may affect the cellular composition of grafts in an important way (Table 3). This affects, e.g., the number of $CD34^+$ cells as well as lymphocytes in the graft. Also, many patient-related factors and previous treatment are important here. The use of CY + G-CSF has constantly led to higher $CD34^+$ cell yields than G-CSF alone mobilization [31, 43, 65]. In addition, chemomobilization also seems to result in higher primitive $CD34^+CD133^+CD38^-$ cell counts in the graft [43]. On the other hand, the use of CY in mobilization decreases the graft total lymphocyte counts [43, 57, 93, 94] as well as the $CD4^+CD3^+$, $CD3^+CD8^+$, $CD19^+$, and NK cell subset counts [43, 95] in comparison to G-CSF alone mobilization. Interestingly, chemomobilization seems to increase the number of regulatory T cells and monocytes in the graft [95].

The addition to PLER to the mobilization also alters the graft cellular composition by increasing the number of all lymphocyte subsets [41, 43]. In G-CSF alone mobilized patients, however, the addition of PLER has been shown to increase only the $CD3^+CD4^+$ lymphocyte compartment significantly [41]. Available data from a long-term follow-up of a randomized study [97] as well as a large registry study organized by EBMT [98] suggest that PLER use for mobilization of blood grafts is associated with comparable patient outcomes than mobilization without PLER.

*Cost-Effectiveness Issues*

The costs of AHCT can be divided into the different phases: mobilization, collection, high-dose therapy, and early posttransplant. Previous studies suggest that the inpatient period associated with high-dose treatment and transplantation is the most expensive part of AHCT, while stem cell mobilization and aphereses constitute less than half the total costs of AHCT [99, 100]. However, outpatient or early-discharge AHCTs performed by some institutions to reduce costs have been reported to be safe and cost-effective [101, 102].

The costs of the mobilization phase usually comprise a relatively small but unpredictable part of the total costs of AHCT. Sung et al. [99] compared real-world outcomes and cost between chemomobilization + G-CSF and G-CSF. Patients who received PLER were excluded from the study. Significantly more $CD34^+$ cells were collected from MM patients mobilized with chemotherapy + G-CSF versus G-CSF alone (13.8 vs. 6.8 × $10^6$ cells/kg), but the mobilization costs were also significantly higher (8,800 vs. 5,600 USD), respectively. There was no significant difference between the mobilization methods in terms of the total median costs of AHCT [99]. However, if the patient mobilizes poorly and needs multiple doses of PLER or needs to be remobilized using PLER, the PLER alone can increase the cost considerably.

We previously published the costs of different phases of AHCT in myeloma patients who underwent mobilization with CY (2 g/m$^2$) + G-CSF or G-CSF alone [100]. PLER was given according to a specific algorithm, only if needed. Mobilization with G-CSF resulted in lower total costs of mobilization and collection than mobilization with CY + G-CSF only in patients requiring one or two apheresis. The total median cost of AHCT was comparable between the groups. Milone et al. [92] previously reported on the cost-effectiveness of preemptive PLER added to mobilizing chemotherapy (CY 4 g/m$^2$) + G-CSF for patients, showing predictive signs of mobilization failure. The cost per patient in the preemptive PLER group was 540 € higher than the cost per patient in the control group. The incremental cost-effectiveness ratio was 40.6 € per 1% increase in the probability of achieving a successful minimal CD34$^+$ cell apheresis harvest (≥2.0 × 10$^6$ CD34$^+$ cells/kg) and 30.7 € per 1% increase in the probability of achieving a successful optimal CD34$^+$ cell apheresis harvest (≥4.0 × 10$^6$ CD34$^+$ cells/kg) [92]. Based on published studies, the cost-effectiveness of different mobilization strategies may differ. However, there is currently no conclusive answer regarding the preferred mobilization method from a cost perspective, and it is necessary to bear in mind the differences in healthcare system structures and funding among countries when assessing the cost-efficacy. Generic PLER [103], where available, will obviously change all cost-effectiveness scenarios.

## Concluding Remarks

Mobilization strategies in myeloma patients intended for AHCT are continuously evolving. There are paucity of data regarding importance of other cell types than CD34$^+$ cells for posttransplant outcome. Optimal strategy should include cost-effectiveness considerations as well as toxicity aspects. Also, local experiences and practices are important here as well as predefined collection targets. At present, cytokine mobilization with preemptive PLER if needed may be the preferred practice in great majority of patients with newly diagnosed MM.

## Conflict of Interest Statement

A.P. reports honoraria from Behring and AbbVie and has participated in Scientific Advisory Board meetings organized by AbbVie, Janssen-Cilag, Novartis, and Takeda. V.V. reports consultancy fees from AbbVie, Amgen, Celgene, Janssen-Cilag, Roche, and Sanofi. R.S. has received Janssen-Cilag Research Funding for FMG-MM01 study, Celgene Research Funding for FMG-MM02 study, Celgene/BMS and Takeda Research Funding for NMSG#23/15 study, and Amgen and BMS Research Funding and compensation as a member of the Scientific Advisory Boards organized by Amgen, BMS, Celgene, Janssen-Cilag, and Takeda and consultancy fees from Amgen, Celgene, Janssen-Cilag, and Sanofi. The other authors declare no conflicts of interest.


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## Author Contributions

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