Peripheral blood stem cell mobilization in multiple myeloma: Growth factors or chemotherapy?

Whitney D Wallis, Muzaffar H Qazilbash

Abstract
High-dose therapy followed by autologous hematopoietic stem cell (HSC) transplant is considered standard of care for eligible patients with multiple myeloma. The optimal collection strategy should be effective in procuring sufficient HSC while maintaining a low toxicity profile. Currently available mobilization strategies include growth factors alone, growth factors in combination with chemotherapy, or growth factors in combination with chemokine receptor antagonists; however, the optimal strategy has yet to be elucidated. Herein, we review the risks and benefits of each approach.

Key words: Multiple myeloma; Stem cell; Mobilization; Growth factors; Chemotherapy

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Core tip: Obtaining an adequate peripheral blood stem cell yield is essential for the successful outcome of autologous hematopoietic stem cell transplant in multiple myeloma. While growth factor mobilization continues to be largely successful, suboptimal collection rates have been noted, particularly as use of novel therapies continue to increase. Chemomobilization remains toxic and has not been associated with better disease control. The newest mobilizing agent, plerixafor, is capable of overcoming suboptimal mobilization even in patients who are at a high risk of mobilization failure. Each mobilization strategy should be selected based on patient specific variables as well as risk factors for mobilization failure.

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stem cell (HSC) transplant (auto-HCT) is considered standard of care for eligible patients with multiple myeloma (MM). MM remains the most common indication for auto-HCT, accounting for over 6000 transplants in the United States alone in 2013[11]. Auto-HCT has been shown to prolong progression-free survival and overall survival in patients with MM[2-4], a benefit that has been maintained even after the availability of immunomodulatory drugs such as thalidomide and lenalidomide[5,6], and proteasome inhibitors like bortezomib. Mobilization and collection of an optimal number of HSC is a fundamental requirement for auto-HCT. The optimal collection strategy should be effective in procuring sufficient HSC while maintaining a low toxicity profile. Currently available mobilization strategies include growth factors alone, growth factors in combination with chemotherapy, or growth factors in combination with chemokine receptor antagonists; however, the optimal strategy has yet to be elucidated. Herein, we review the data surrounding each approach.

SOURCE OF HSCs
Historically, bone marrow (BM) was used as the sole source of HSC for transplantation[7,8]. However, the ability to mobilize HSC to peripheral blood (PB) has eliminated the risk of general anesthesia, intubation, and painful aspirations associated with BM harvesting. Peripheral blood stem cell (PBSC) collection can be performed in the outpatient setting with a shorter recovery time. Additionally, use of PBSC reduces time to hematopoietic reconstitution, hospital stay, and need for transfusions[9-11]. Consequently, PB has largely replaced BM as the source of HSC for auto-HCT[12].

PBSC DOSE
The number of CD34 expressing mononuclear cells in PBSC collection correlates well with engraftment kinetics and thus is used as a surrogate marker of HSC[13-16] (Figure 1). A dose of > 2 million CD34+ cells per kilogram (cells/kg) is considered the minimum acceptable dose for timely engraftment[17]. However, larger cell doses have been associated with a more rapid time to platelet and neutrophil recovery[18,19] and therefore ≥ 3-5 million CD34 cells/kg is considered an optimal target[20,21].

PBSC MOBILIZATION APPROACHES
HSC primarily reside in the BM and account for 1%-4% of all mononuclear cells[13,15,22]. Retention of HSC in the BM is dependent on interactions between cell adhesion molecules on the surface of HSC, such as chemokine receptor 4 and very late antigen 4 (VLA4), and BM stromal factors, such as vascular cell adhesion molecule (VCAM-1) and stromal cell-derived factor-1 (SDF-1)[23]. Mobilization of HSC from BM to PB is the result of induced chemical disruption of these interactions between HSC and BM stroma. Cytokines, such as granulocyte-colony stimulating factor (G-CSF), and chemotherapy drugs like cyclophosphamide play an important role in releasing HSC from their niches in the BM[23-25] (Figure 2).

Growth factors alone
Historically, growth factors alone have been largely successful in mobilizing an adequate cell yield in MM patients undergoing auto-HCT[26,27] (Table 1). G-CSF has well established kinetics as well as favorable toxicity and cost profiles[26-30] but has been associated with suboptimal mobilization in over 20% of MM patients[31-33]. Data regarding a dose-response relationship between G-CSF and CD34+ cell yield is discordant but doses up to 40 μg per kilogram per day (μg/kg per day) have been studied[34-36]. A widely accepted G-CSF dose for PBSC mobilization is 10 μg/kg per day as single or divided doses.

Other growth factors such as granulocyte-macrophage-colony stimulating factor (GM-CSF), pegylated G-CSF, and tbo G-CSF have also been studied for PBSC mobilization in MM patients[37-42]. When G-CSF was compared to GM-CSF in MM patients, CD34+ cell yield was similar between

![Figure 1](http://www.nature.com/bmt/index.html)
the two groups, but GM-CSF-mobilized patients had a longer duration of neutropenia\(^43\). In-vitro data suggest that combination of G-CSF + GM-CSF may improve PBSC yield\(^44,45\), but clinical trial data has not found a significant difference in CD34\(^+\) cell yield or time to hematopoietic recovery with combination therapy\(^41\).

Pegylated (PEG) filgrastim, a covalent conjugate of G-CSF and monomethoxy-polyethylene glycol, has a terminal half-life of 15-80 h, which enables less frequent administration compared to G-CSF. Given as a single 12 mg injection followed by PBSC collection, all MM patients who received PEG filgrastim successfully collected their target CD34\(^+\) cells/kg dose\(^39\). Similarly, a multi-dose regimen of PEG filgrastim had a higher CD34\(^+\) cells yield on first apheresis compared to G-CSF, but no differences in overall cell yield was observed\(^46\). Its convenient dosing schedule makes it an attractive option for PBSC mobilization.

Tbo-filgrastim is a non-glycosylated recombinant methionyl human G-CSF manufactured using the bacterium strain E. coli K802\(^47\). While not FDA approved for stem cell mobilization, retrospective data in MM patients found no difference in overall cell yield, number of apheresis sessions required for collection, nor need for rescue therapy with plerixafor\(^38,48\).

Myelosuppressive chemotherapy

Transient circulation of PBSC occurs during the recovery phase of chemotherapy-induced pancytopenia\(^22,49,50\) and is augmented by growth factor support\(^22\) (Table 2). This

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Table 1  Growth factor mobilization

| Ref.                  | Disease | Collection strategy | n  | CD34\(^+\) yield (× \(10^6\) cell/kg): Median (range) | Failure a (%) |
|-----------------------|---------|---------------------|----|-------------------------------------------------------|---------------|
| Desikan et al\(^26\)  | MM      | G-CSF 10-16 \(\mu\)g/kg per day | 117 | 6.2 (0.6-34.1)                                       | NR            |
| Kröger et al\(^27\)   | MM      | G-CSF 10-24 \(\mu\)g/kg per day | 25  | 3.8 (0.3-17)                                        | 3 (12)        |
| Popat et al\(^28\)    | MM      | G-CSF 30 \(\mu\)g/kg per day    | 302 | NR                                                    | 9%            |
| Pusic et al\(^29\)    | MM      | G-CSF 10 \(\mu\)g/kg per day    | 384 | 4.6                                                  | 24 (6.3)      |
|                       | NHL HD  | G + C                | 17  | 8.5                                                  | 1 (5.9)       |
| Weaver et al\(^30\)   | BC      | G-CSF 10 \(\mu\)g/kg per day | 14  | 0.6 (0.1-2.8)                                       | NR            |
|                       |         | G-CSF 20 \(\mu\)g/kg per day | 13  | 1 (0.2-5.2)                                         |               |
|                       |         | G-CSF 30 \(\mu\)g/kg per day | 14  | 2.4 (0.6-6.8)                                       |               |
|                       |         | G-CSF 40 \(\mu\)g/kg per day | 14  | 1.4 (0.1-4.8)                                       |               |
|                       | BC      | G-CSF 250 \(\mu\)g/m\(^2\) per day | 16 | 4.78 (3.02-10.68)                                 | 0             |
|                       | HD      | G-CSF 250 \(\mu\)g/m\(^2\) per day | 15 | 8.01 (3.17-29)                                    | 0             |
| Weisdorf et al\(^32\) | NHL     | GM-CSF 10 \(\mu\)g/kg per day | 26  | 21.45 (1.63-182.91)                                | NR            |
|                       | HD      | G-CSF 10 \(\mu\)g/kg per day + | 24  | 14.33 (0.56-102.08)                                |               |
|                       | MM      | GM-CSF 5 \(\mu\)g/kg per day | 19  | 8.4 (4.1-15.8)                                      | 0             |
|                       |         | PEG 12 mg × 1         |     | 8.1 (5.17-19.2)                                    | 0             |

MM: Multiple myeloma; G-CSF: Granulocyte colony stimulating factor; NR: Not reported; BC: Breast cancer; NHL: Non-hodgkin’s lymphoma; GM-CSF: Granulocyte macrophage colony stimulating factor; HD: Hodgkin’s disease; GCT: Germ cell tumor; PEG: Pegylated filgrastim.

The figures illustrate the bone marrow microenvironment: A) at physiologic state and effects of (B) granulocyte colony stimulating factor mobilization and (C) Plerixafor mobilization. Reprinted from Journal of Cellular Biochemistry, Vol 99/edition 3, Bruno Nervi, Dan C. Link, John F DiPersio, Cytokines and Hematopoietic Stem Cell Mobilization, 690-705, 2010, with permission from Wiley\(^26\). G-CSF: Granulocyte colony stimulating factor; HSC: Hematopoietic stem cell; SDF-1: Stromal cell-derived factor-1; VCAM-1: Vascular cell adhesion molecule.
process, chemomobilization (CM), provides not only higher cell yields than G-CSF alone, but also affords anti-myeloma activity. Cyclophosphamide (CY) 2-4 g/m², either alone or in combination with other chemotherapeutic agents, is commonly used in CM and has been a successful mobilization technique even in patients who underwent induction therapy with novel agents. The impact of increased doses of CY on PBSC yields has shown conflicting results but was consistently associated with a longer duration of neutropenia as well as the use of antibiotics and blood products. No additional impact on cell yield or objective response rate has been seen with the use of combination chemotherapy followed by growth factor (G-CSF) (Table 3). Furthermore, despite the potential benefit of cyto reduction, CM has not been associated with a better disease control or survival in MM.

**Chemokine receptor antagonist**

The newest mobilizing agent, plerixafor, rapidly and reversibly inhibits chemokine receptor CXCR4 on HSC, thereby preventing the binding of SDF-1α to CXCR4. Synergistic effect on PBSC mobilization is observed when plerixafor is given in combination with G-CSF. A phase III randomized, placebo controlled trial in MM patients compared mobilization with plerixafor + G-CSF to placebo + G-CSF. Use of plerixafor resulted in an increase in proportion of patients that were able to collect a cell yield of ≥6 × 10⁶/kg with fewer apheresis procedures compared to the G-CSF only group. Transplant outcomes were similar between groups. Plerixafor can overcome suboptimal mobilization seen with conventional chemotherapy agents. Plerixafor can overcome suboptimal mobilization seen with prolonged prior lenalidomide therapy and other conventional chemotherapies.

### Table 2 Growth factors following chemotherapy

| Ref.      | Disease | Collection strategy | n  | CD34⁺ yield (× 10⁴ cell/kg): Median (range) | Failure rates n (%) |
|-----------|---------|---------------------|----|--------------------------------------------|----------------------|
| Weaver et al[65] | MM ML | G-CSF 6 µg/kg per day | 49 | 12 (0.1-54) | 2 (4.3) |
| Gojo et al[61] | MM | G-CSF 10 µg/kg per day | 35 | 16.4 (1.1-71.7) | NR |
| Hamadani et al[67] | MM | G-CSF 250 µg/m² per day | 12 | 7.4 (4.9-38) | 0 |
| Tricot et al[69] | MM | G-CSF 8.5 µg/kg per day | 12 | 10.1 (5.47) | 0 |

**Table 3 Impact of chemotherapy on cell yield and morbidity**

| Ref.      | Collection strategy | n  | CD34⁺ yield (× 10⁴ cell/kg): Median (range) | Hospital days: median (range) | Infection (%) | Transfusions (% platelet/PRBC) |
|-----------|---------------------|----|--------------------------------------------|-----------------------------|--------------|--------------------------------|
| Desikan et al[62] | CY 6 g/m² + G-CSF 6 µg/kg per day | 22 | 33.4 (NR) | No difference | 18 | 86/86 |
| Alegre et al[63] | CY 4 g/m² + GM-CSF | 18 | 6.8 (1.8-34.8) | 21 (16-34) | 11 | 33.3/27.7 |
| Jantunen et al[64] | CY 4 g/m² + G-CSF | 42 | 14.4 (1.7-66.8) | 22 (13-55) | 16.7 | 26.2/52.4 |
| Gojo et al[65] | CY 1.5 g/m² + GM-CSF | 42 | 5.6 (0.9-19) | 5 (5-12) | NR | 0/28 |
| Hamadani et al[67] | CY 3-4 g/m² + G-CSF | 35 | 16.6 (2.8-2) | 4 (1-9) | NR | 21.8/34.5 |
| Hiwase et al[68] | CY 1-2 g/m² + G-CSF | 61 | 5.17 | 6 (3-18) | 5 | No difference |

1st apheresis session. PRBC: Packed red blood cells; CY: Cyclophosphamide; G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; NR: Not reported; HGF: Hematopoietic growth factor; VP-16: Etoposide.
PB CD34⁺ count on day 4 is less than a predetermined threshold (10 × 10⁶/L-10 × 10⁹/L). Such strategies are associated with fewer mobilization failures when compared to traditional mobilization methods and appear to be cost effective [76-79]. Additional methods of cost reduction, namely the use of tbo-filgrastim, in combination with plerixafor has been studied. Prospective data in MM patients found similar overall cell yields without any mobilization failures [80].

PREDICTORS OF SUBOPTIMAL MOBILIZATION

Mobilization failure is generally defined as the inability to procure 2 × 10⁶ CD34⁺ cells/kg in 4 apheresis sessions. Despite recent advances in PBSC collection strategies, failure to obtain an adequate cell dose continues to delay and preclude auto-HCT in otherwise suitable transplant candidates. Factors associated with inadequate HSC mobilization in MM patients include: Thrombocytopenia [81], age > 60 years [36,38,52], extensive treatment course [17], prior radiotherapy, prior exposure to alkylating agents [17,63], and prolonged use of lenalidomide [20,21,31,34,35]. Such factors have been incorporated in consensus guidelines on stem cell mobilization (Table 4).

Lenalidomide’s impact on cell yield is of particular concern due to its common use in frontline therapy [86]. While known to cause neutropenia and thrombocytopenia, the exact mechanism of lenalidomide induced myelosuppression is not fully known. In one study, lenalidomide was associated with a significant decrease in expression of transcription factor PU.1, which is critical for myeloid maturation [87]. In another study, lenalidomide-treated patients were found to have decreased BM CD34⁺ cells after six cycles of therapy [88]. This supports the literature that identifies lenalidomide as a risk factor for suboptimal stem cell collection and suggests that transplant eligible patients receiving lenalidomide should proceed to mobilization as early as feasible.
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Did the patient have PR to induction therapy?

| Yes | Add plerixafor or administer additional CM |
|-----|------------------------------------------|
| No  | G-CSF 10-16 μg/kg daily  |
|     | CM with cyclophosphamide 2-4 g/m² |

**Figure 3** Mobilization strategies at authors’ institution. CM: Chemomobilization; G-CSF: Granulocyte colony stimulating factor.

Despite identification of risk factors for poor mobilization, predictive algorithms have not correctly identified poor mobilizers. The best predictor of adequate CD34+ cell collection is the pre-collection PB CD34+ cell count. A strong correlation exists with PB CD34+ cell count and the final CD34+ cell collection (Figure 1). PB CD34+ count ≥ 20 × 10^6 CD34+ cells/mL was associated with an adequate HSC collection in 94% of patients.

**CONCLUSION**

In summary, obtaining an adequate PBSC yield is essential for the successful outcome of auto-HCT in MM. Each mobilization strategy reviewed here has its own advantages and disadvantages (Table 5) and should be selected based on patient specific variables. Current practice at the authors’ institution is detailed in Figure 3; however, practitioners should be cognizant of risk factors for mobilization failure and utilize appropriate algorithms to optimize stem cell collection.

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