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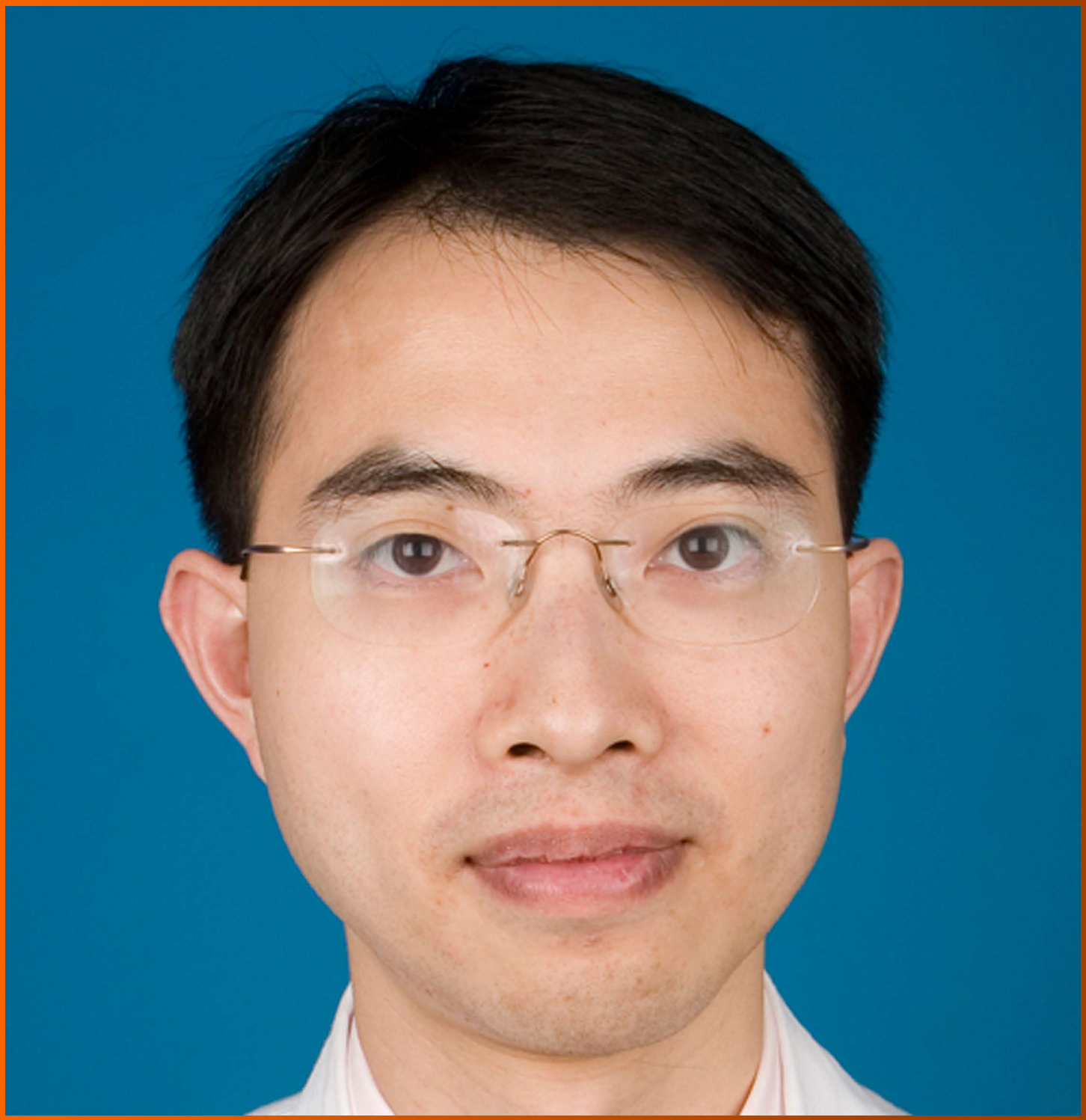

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REVIEW

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

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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

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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INTRODUCTION

High-dose therapy followed by autologous hematopoietic

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[1]. 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).

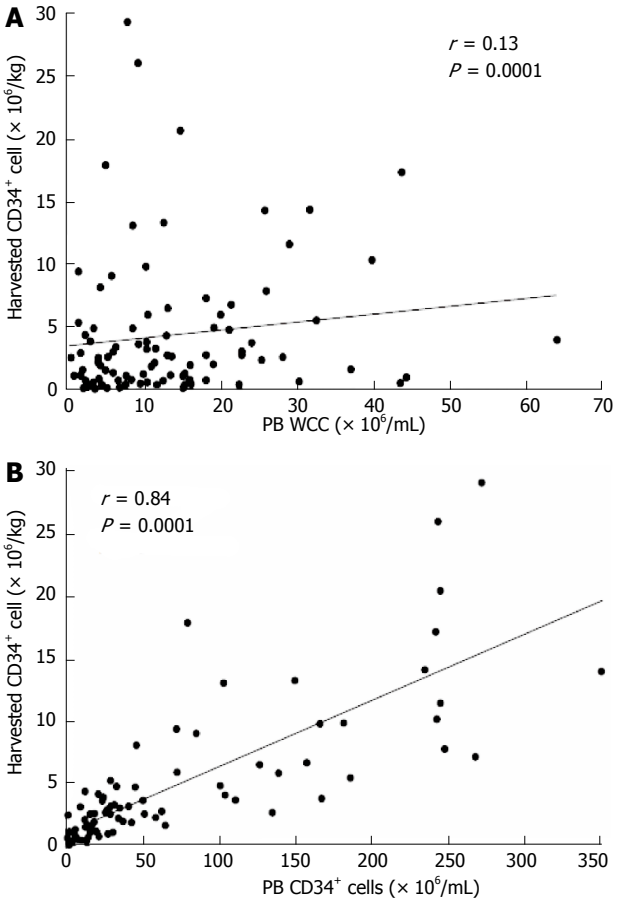

Figure 1 Correlation of harvested $CD34^+$ cells counts with white blood cell count and peripheral blood $CD34^+$ cell count. A: Correlation of harvested $CD34^+$ cells counts with white blood cell count; B: Correlation of harvested $CD34^+$ cells counts with peripheral blood $CD34^+$ cell count. Reprinted by permission from Macmillan Publishers Ltd: *Bone Marrow Transplant* 1997[16]. http://www.nature.com/bmt/index.html.

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[28-30] 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

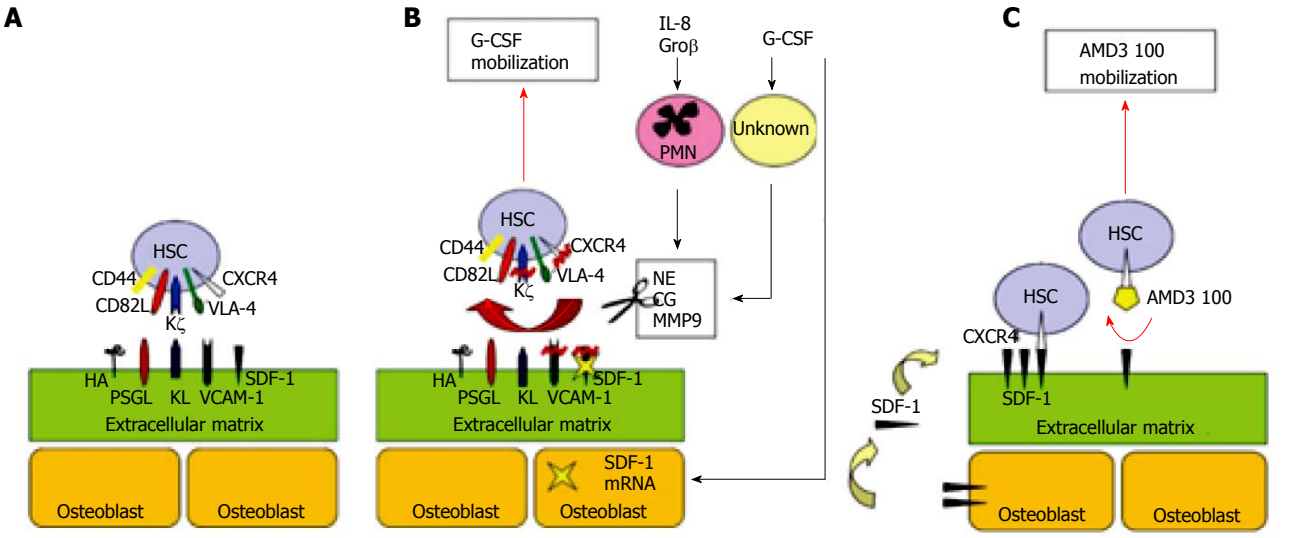

Figure 2 Bone marrow microenvironment (A) at physiologic state and effects of (B) granulocyte colony stimulating factor mobilization and (C) Plerixafor mobilization. Reprinted from *Journal of Cellular Biochemistry*, Vol 99/edition 3, Bruno Nervi, Dan C. Link, John F DiPersio, Cytokines and Hematopoietic 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.

Table 1 Growth factor mobilization

Ref.	Disease	Collection strategy	*n*	CD34$^+$ yield (× 10^{-6} cell/kg): Median (range)	Failure *n* (%)
Desikan *et al*[26]	MM	G-CSF 10-16 μg/kg per day	117	6.2 (0.6-34.1)	NR
Kröger *et al*[27]	MM	G-CSF 10-24 μg/kg per day	25	3.8 (0.3-17)	3 (12)
Popat *et al*[31]	MM	G-CSF	302	NR	9%
Pusic *et al*[90]	MM	G-CSF 10 μg/kg per day	384	4.6	24 (6.3)
	NHL HD	G + C	17	8.5	1 (5.9)
Weaver *et al*[34]	BC	G-CSF 10 μg/kg per day	14	0.6 (0.1-2.8)	NR
		G-CSF 20 μg/kg per day	13	1 (0.2-5.2)	
		G-CSF 30 μg/kg per day	14	2.4 (0.6-6.8)	
		G-CSF 40 μg/kg per day	14	1.4 (0.1-4.8)	
Weisdorf *et al*[42]	NHL	GM-CSF 250 μg/m^2 per day	16	4.78 (3.02-10.68)	0
	HD	G-CSF 250 μg/m^2 per day	15	8.01 (3.17-29)	0
Spitzer *et al*[41]	BC GCT	GCSF 10 mcg/kg per day	26	21.45 (1.63-182.91)	NR
	NHL HD	GCSF 10 mcg/kg per day +	24	13.33 (0.56-102.08)	
	MM	GM-CSF 5 mcg/kg per day			
Hosing *et al*[39]	MM	PEG 12 mg × 1	19	8.4 (4.1-15.8)	0
		G-CSF 10 μg/kg per day	8	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 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

Table 2 Growth factors following chemotherapy

Ref.	Disease	Collection strategy	*n*	$CD34^+$ yield ($\times 10^{-6}$ cell/kg): Median (range)	Failure rates *n* (%)
Weaver *et al*[91]	MM ML	G-CSF 6 μg/kg per day	49	12 (0.1-54)	2 (4.1)
	BC	GM-CSF 250 μg/m^2 per day	49	5.4 (0.02-64)	4 (8.2)
		GM-CSF × 5 d then G-CSF 6 μg/kg per day	52	10.5 (0.4-96)	1 (1.9)
Arora *et al*[43]	MM	G-CSF 250 μg/m^2 per day	35	16.4 (1.1-71.7)	NR
		GM-CSF 250 μg/m^2 per day	37	12.8 (0.4-94.5)	
Tricot *et al*[46]	MM	PEG 6 mg q7d × 2	97	NR; no difference	NR
		G-CSF 10 μg/kg per day	140		
Fruehauf *et al*[92]	MM	PEG 12 mg × 1	26	9.7 (4.9-40.5)	3 (11.5)
Steidl *et al*[93]	MM	PEG 12 mg × 1	12	7.4 (4.9-38)	0
		G-CSF 8.5 μg/kg per day	12	10.8 (5-87)	0

MM: Multiple myeloma; ML: Malignant lymphoma; BC: Breast cancer; G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; NR: Not reported; NHL: Non-hodgkin's lymphoma; PEG: Pegylated filgrastim.

Table 3 Impact of chemotherapy on cell yield and morbidity

Ref.	Collection strategy	*n*	$CD34^+$ yield ($\times 10^{-6}$ cell/kg): median (range)	Hospital days: median (range)	Infection (%)	Transfusions (%) platelet/PRBC
Desikan *et al*[32]	CY 6 g/m^2 + G-CSF 6 μg/kg per day	22	33.4 (NR)	No difference	18	86/86
	G-CSF 16 μg/kg per day	22	5.8 (NR)		0	18/55
Alegre *et al*[51]	CY 4 g/m^2 + GM-CSF	18	6.8 (1.8-34.8)	21 (16-34)	11	33.3/27.7
	G-CSF 10 μg/kg per day	22	4.85 (2.1-10.05)	0	0	0/0
Fitoussi *et al*[60]	CY 7 g/m^2 + HGF	74	8.6 (0.4-166)	15 (9-34)	17.6	75.7/94.6
	CY 4 g/m^2 + HGF	42	13.4 (0.7-66.8)	22 (13-55)	16.7	26.2/52.4
Jantunen *et al*[61]	CY 4 g/m^2 + G-CSF 5-10 μg/kg per day	32	4.9 (0.8-47.4)[1]	9 (6-14)	NR	34/53
	CY 1.2-2 g/m^2 + G-CSF 5 μg/kg per day	42	5.6 (0.9-19)[1]	5 (3-12)	NR	0/28
Gojo *et al*[65]	CY 4.5 g/m^2 + G-CSF	28	21.38 (0-106.8)	8 (4-24)	25	57/NR
	CY 4.5 g/m^2 + VP-16 + G-CSF	49	22.39 (0-114.71)	7 (3-68)	53	67/NR
Hamadani *et al*[94]	CY 3-4 g/m^2 + G-CSF	55	16.6 (2-82)	4 (1-9)	NR	21.8/34.5
	CY 1.5 g/m^2 + G-CSF	68	7.5 (0-18)	3 (1-5)	NR	2.9/8.8
Hiwase *et al*[95]	CY 3-4 g/m^2 + G-CSF	26	7.71	7 (3-22)	19	No difference
	CY 1-2 2 g/m^2 + G-CSF	61	5.17	6 (3-18)	5	

[1]1st apheresis session. PRBC: Packed red blood cells; CY: Cyclophosphamide; G-CSF: Granulocyte colony stimulating factor; NR: Not reported; HGF: Hematopoietic growth factor; VP-16: Etoposide.

process, chemomobilization (CM), provides not only higher cell yields than G-CSF alone, but also affords anti-myeloma activity[32,51-54]. Cyclophosphamide (CY) 2-4 g/m^2, 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[31,55-59]. 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[54,60-64]. No additional impact on cell yield or objective response rate has been seen with the use of combination chemotherapy followed by growth factor[55,65] (Table 3). Furthermore, despite the potential benefit of cytoreduction, CM has not been associated with a better disease control or survival in MM[32,51,52,66-68].

Chemokine receptor antagonist

The newest mobilizing agent, plerixafor, rapidly and reversibly inhibits chemokine receptor CXCR4 on HSC, thereby preventing the binding of SDF-1a to CXCR4. Synergistic effect on PBSC mobilization is observed when plerixafor is given in combination with G-CSF[69,70]. 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 $\geqslant 6 \times 10^6$/kg with fewer apheresis procedures compared to the G-CSF only group. Transplant outcomes were similar between groups[71]. Plerixafor can overcome suboptimal mobilization seen with prolonged prior lenalidomide therapy and other conventional chemotherapy agents[72,73]. Following failed attempts to mobilize, MM patients received a combination of G-CSF and plerixafor. In this population, at least 70% of patients were able to achieve a sufficient PBSC yield, without any evidence of tumor mobilization[73,74]. Plerixafor is successful when used as the initial mobilization strategy but at an increased drug acquisition cost and in patients that presumably could have attained an appropriate cell yield with G-CSF alone[75,76].

Risk adaptive strategies use initial mobilization with G-CSF alone and utilize plerixafor only in patients whose

Table 4 International Myeloma Working Group Consensus guidelines and recommendations on mobilization in malignant lymphoma[20]

Strategy	Recommendations
Mobilization	
G-CSF alone	Limit use to patients Treated with ⩽ 1 line of therapy Never exposed to melphalan Received ⩽ 4 cycles of lenalidomide Use doses from 10-16 μg/kg per day Monitor PB $CD34^+$ count
Chemomobilization + G-CSF	Limit to patients who have not adequately responded to salvage therapy
Plerixafor	Suitable for all patients particularly if goals include Highest cell yield obtainable Fewer apheresis sessions
Remobilization	
Plerixafor	P + G-CSF or P + CM + G-CSF
Chemomobilization	Acceptable in patients who failed cytokine mobilization
Bone marrow harvest	Use as third-line option in patients in whom ASCT is compelling

PB$CD34^+$: Peripheral blood $CD34^+$ cells; P + G-CSF: Plerixafor + granulocyte colony stimulating factor; P + CM + G-CSF: Plerixafor + chemomobilization + granulocyte colony stimulating factor.

Table 5 Advantages and disadvantages of mobilization strategies

Mobilization strategy	Advantages	Disadvantages
Growth factor	Cost effective Successful mobilization in most patients Predictable schedule	No anti-myeloma effect Multiple injections and collections Potential sub-optimal yield
CM	Anti-myeloma effect Increased cell yield Fewer apheresis sessions	Cytopenias Infection risk Hospital admission Potential transfusion requirement Unpredictable count recovery
Plerixafor	Rapid kinetics Increased cell yield Fewer apheresis sessions	Higher drug cost

CM: Chemomobilization.

PB $CD34^+$ count on day 4 is less than a predetermined threshold (10×10^6/L-10×10^9/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 2×10^6 $CD34^+$ 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[36,58,82], extensive treatment course[17], prior radiotherapy, prior exposure to alkylating agents[17,83], and prolonged use of lenalidomide[20,21,31,84,85]. 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.

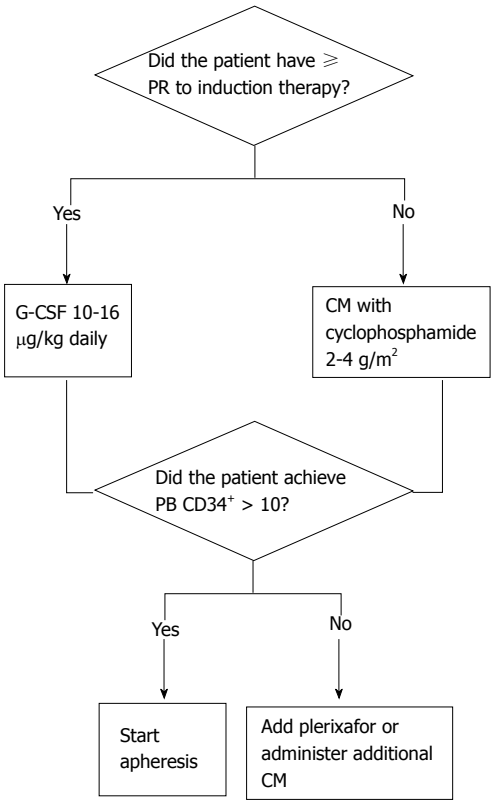

Figure 3 Mobilization strategies at authors' institution. CM: Chemomobilization; G-CSF: Granulocyte colony stimulating factor.

Despite identification of risk factors for poor mobilization, predictive algorithms have not correctly identified poor mobilizers[89]. 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 ⩾ 20×10^3 $CD34^+$ cells/mL was associated with an adequate HSC collection in 94% of patients[16,90].

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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