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ASBMT Guideline

Peripheral Blood Progenitor Cell Mobilization for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation

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A B S T R A C T

Peripheral blood progenitor cell mobilization practices vary significantly among institutions. Effective mobilization regimens include growth factor alone, chemotherapy and growth factor combined, and, more recently, incorporation of plerixafor with either approach. Many institutions have developed algorithms to improve stem cell mobilization success rates and cost-effectiveness. However, an optimal stem cell mobilization regimen has not been defined. Practical guidelines are needed to address important clinical questions, including which growth factor is optimal, what chemotherapy and dose is most effective, and when to initiate leukapheresis. We present recommendations, based on a comprehensive review of the literature, from the American Society of Blood and Marrow Transplantation.

INTRODUCTION

Hematopoietic cell transplantation (HCT) has become an increasingly important therapy for patients with hematologic malignancies. In the past several decades, the utilization of both autologous and allogeneic HCTs for adult and pediatric populations has risen significantly. Peripheral blood progenitor cell (PBPC) mobilization and collection is a critical part of the HCT procedure.

Mobilization and collection practices vary widely. PBPC mobilization and collection processes require involvement and coordination of various departments, including the clinical transplant program, therapeutic apheresis, and flow cytometry, and cell processing laboratories. Important considerations regarding the choice of mobilization regimen also include patient safety, efficacy and reliability of the regimen, physician familiarity of the regimen, patient convenience, and cost-effectiveness. These variables have led to tremendous heterogeneity in practices. Institutions have adapted strategies according to their preference and resource availability. No standard approach has been established, and an optimal regimen has not been defined.

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Recently, consensus guidelines addressing autologous stem cell mobilization strategies have been published [1]. Recognizing the need for a more standardized approach and best practice recommendations for both autologous and allogeneic PBPC mobilization, the Practice Guidelines Committee of the American Society for Blood and Marrow Transplantation assembled a working group to address important questions in this evolving field, the answers to which provide clinical guidelines based on the best available evidence.

METHODS

The working group included experts in clinical transplantation and apheresis. A list of important questions relevant to PBPC mobilization and collection was generated. A comprehensive and critical review of relevant published literature was then performed to address those questions. We screened for publications in the PubMed database by including the search terms "stem cell mobilization," "growth factor stem cell mobilization," "plerixafor stem cell mobilization," "chemotherapy stem cell mobilization," "pediatric stem cell mobilization," "mobilization algorithm," and other search terms pertinent to the questions being addressed.

Relevant references in the publications were also identified and reviewed. Both retrospective and prospective studies were included. Meeting abstracts, data from non–peer-reviewed journals, review articles, and studies with incomplete data were excluded. Studies based on small sample size (<25 patients) were included when they constituted the only available data or were otherwise of significant impact. Much of these data are old, some are of poor quality, and only few are randomized, prospective studies.

One hundred eleven articles most pertinent to the proposed questions were identified. These articles were then graded according to level of evidence and strength of recommendation [2]. Technical aspects of stem cell mobilization and collection will be addressed in future guidelines to be published by the American Association of Blood Banks.

GUIDELINES

A summary of recommendations in the format of frequently asked questions is also provided in Tables 1, 2, and 3.

Allogeneic Progenitor Cell Transplant

Question 1: What is the best myeloid growth factor and dose schedule for mobilization for adult donors?

Single-agent filgrastim (granulocyte colony-stimulating factor [G-CSF]) is the preferred growth factor for mobilizing peripheral blood progenitor cells (PBPCs) in healthy adult donors. The recommended dose is 10 μg/kg body weight/day, either as a single or split dose. Several studies have demonstrated the superiority of G-CSF as a single agent compared with granulocyte macrophage (GM)-CSF (sargramostim) or combination growth factor support [3-15]. Equivalent split dosing (5 μg/kg twice daily) or higher split dosing (12 μg/kg twice daily) has been reported to result in higher collection yields with shorter collection times; however, the toxicities of bone pain, fatigue, and headaches were more frequent, and costs were higher [7-10]. As a result, most centers do not use higher doses. Similarly, when G-CSF is compared with combination growth factor support, although a higher number of cells may be collected, there are increased toxicities and no overall benefit [11-13]. A prospective randomized study recently compared G-CSF alone to G-CSF plus GM-CSF and reported differential graft content without significant differences in survival [13]; the potential impact of graft composition differences on other outcomes will need to be explored.

Filgrastim (nonglycosylated G-CSF), which is most commonly used in the United States, has been compared with lenograstim (glycosylated G-CSF), which is widely used in Europe, with similar reported outcomes [14,15]. Although the longer acting pegylated G-CSF (pegfilgrastim) is effective, little data support its use given the possibly increased toxicities and higher costs [16,17].

Plerixafor binds to and blocks the chemokine receptor type 4 on stem cells that are thereby unanchored and able to enter the bloodstream. Results of mobilization with single-agent plerixafor have been reported, but the current data, at best, indicate no benefit over G-CSF alone. An ongoing Center for International Blood and Marrow Transplant Research study is enrolling and evaluating single-agent plerixafor in donors [18].

For adult volunteer unrelated donors, the National Marrow Donor Program (NMDP) performs PBSC collections under an NMDP-sponsored research protocol, operated under an Investigational New Drug application with the US Food and Drug Administration. Under this protocol, G-CSF is administered for 4 or 5 consecutive days at a daily dose of 10 μg/kg. The NMDP also recommends that PBSC collections do not exceed a maximum blood volume of 24 liters, collected over 1 or 2 consecutive days, unless approved in advance by the NMDP medical director.

Question 2: Is PBPC mobilization with growth factors safe for pediatric donors, and, if so, what is the best myeloid growth factor and dose schedule?

PBPC collection is safe in healthy pediatric donors, and target $CD34^+$ cell yields can be achieved.

The Pediatric Blood and Marrow Transplant Consortium conducted a retrospective analysis on the safety and efficacy of PBSC donation by 201 pediatric sibling donors from 22 institutions. The results showed that target $CD34^+$ cell yields were successfully achieved. Younger age, more days of apheresis, and male gender were predictive of higher cell yields. Growth factor–induced pain was reported in fewer than 15% of donors. Most donors required central venous catheter placement, but approximately one third of children between ages 7 and 12 years could be collected via peripheral access. Children weighing less than 20 kg were subjected to a single blood product exposure for priming of the apheresis machine. Complications were generally limited and mild [19].

There are limited data comparing mobilization regimens in children. However, the most common approach uses G-CSF at 10 μg/kg/day as a single daily dose or in 2 divided doses [18-23].

Question 3: What are the target $CD34^+$ cell doses for collection and infusion for adult patients?

In allogeneic HCT, the importance of cell dose on transplantation outcomes has been demonstrated by multiple studies. Although the absolute lower threshold to guarantee engraftment is not known, the generally accepted minimal cell dose is 2×10^6 $CD34^+$ cells/kg. Although some studies have demonstrated that successful engraftment has occurred at doses as low as 0.75×10^6 $CD34^+$ cells/kg, neutrophil and, particularly, platelet engraftment were delayed [24].

Higher doses result in faster engraftment and reduced rates of infection and nonrelapse mortality. However, beyond a certain threshold, there may be no added benefit and a possible increased risk of chronic graft-versus-host disease (GVHD) [24-32]. A target $CD34^+$ cell dose between 4 and 5×10^6 $CD34^+$ cells/kg seems most reasonable based on available data.

In 3 large studies of matched sibling donor transplantation, higher cell doses were associated with faster

Table 1
Allogeneic Donors

	Recommendation	Grade of Recommendation	References	Comments
What is the best myeloid growth factor and dose schedule for mobilization for adult patients?	Filgrastim (Neupogen®, G-CSF) 10 μg/kg/day, as a single dose, or 5 μg/kg twice daily, with leukapheresis beginning on the fifth day	A	3-10	Split dosing has been reported to increase cell yield but is less convenient for donors and is not typically done.
	Sargramostim (Leukine®, GM-CSF)	B	11-13	The use of GM-CSF as single agent is not advised because $CD34^+$ cell yields were lower compared with G-CSF and donors required more leukapheresis for adequate collection.
	Lenograstim (Granocyte®)	B	14-15	No statistical difference in major outcomes between single-agent filgrastim and lenograstim. Lenograstim not available in the US.
	Pegfilgrastim (Neulasta®) 6-12 mg/d as a single dose	B	16-17	There are few reports of pegfilgrastim as a single agent but not widely used.
	Plerixafor (Mozobil®) 240 μg/kg as single agent	C	18	There is currently only recent and therefore insufficient evidence to more strongly support the use of plerixafor for this indication.
Is stem cell mobilization safe and effective for pediatric patients? What is the best myeloid growth factor and dose schedule for pediatric patients?	G-CSF 10 μg/kg/day either as a single daily dose, with leukapheresis beginning on the fifth day	C	19-23	Peripheral blood stem cell mobilization with growth factor support is safe for pediatric donors.
What are the target $CD34^+$ doses for collection and infusion for adult patients?	*For infusion:* Optimal: $\geq 4 \times 10^6$ $CD34^+$ cells/kg Maximum: 8×10^6 $CD34^+$ cells/kg *For collection:* Minimum: 2×10^6 $CD34^+$ cells/kg	C	24-32	A minimum threshold has not been identified. Although 2×10^6 $CD34^+$ cells/kg is generally accepted as the minimum goal, successful transplantation has occurred at much lower doses. However, with lower doses, there is increased risk delayed engraftment. Several studies have shown that higher doses of $CD34^+$ cell infusions are associated with faster engraftment. In the setting of matched sibling donor transplants, some studies have shown increased risk for extensive chronic GVHD with $CD34^+$ cell doses above 8×10^6 cells/kg. For matched unrelated donor transplants, higher cell doses have not been associated with worsening GVHD; however, $CD34^+$ cell doses above 9×10^6 cells/kg did not result in any further survival benefit.
What are the target $CD34^+$ cells doses for collection and infusion for *pediatric* patients?	*For infusion:* Minimum: 2.4×10^6 $CD34^+$ cells/kg *For collection:* Minimum: 2×10^6 $CD34^+$ cells/kg	C	33-36	Little data regarding optimal dose. Higher stem cell dose results in improved engraftment.
What type of venous access is recommended?	*For adult patients:* Antecubital venous access is preferred. If peripheral access is not possible, central venous access may be placed by image guidance.	C	37-41	
	For pediatric patients: Most small children require central venous catheter placement under general anesthesia. However, children aged between 7 and 12 years should still be assessed for possible use of peripheral vein access.	C	19, 20	

Table 2
Autologous Donors: Initial Mobilization Attempt

	Recommendation	Strength of Recommendation	References	Comments
What is the optimal myeloid growth factor and dose schedule for initial mobilization for adult patients?	*For growth factor only stem cell mobilization:*			
	Filgrastim 10 μg/kg/day, as a single dose, with leukapheresis beginning on the fifth day	A	42-46	This dose is most commonly used.
	Pegfilgrastim 12 mg, as a single dose, with leukapheresis beginning when the peripheral blood stem cell count is adequate (as defined below)	C	47	Although effective, not adopted by many centers.
	Plerixafor and filgrastim: filgrastim 10 μg/kg/day as a single dose with plerixafor 240 μg/kg in the afternoon or evening before beginning leukapheresis (on day 5)	A	48-50	Because plerixafor can be prohibitively expensive, many centers limit its use to those who are at highest risk for mobilization failure.
	For chemotherapy combined with growth factor for stem cell mobilization:			
	Filgrastim 5-10 μg/kg/day, as a single dose, beginning at least 24 h after completion of chemotherapy, and then leukapheresis beginning when the peripheral blood stem cell count or WBC count is adequate	A	51, 54-57	Although side effect profiles and other outcomes are similar, filgrastim is more commonly used than pegfilgrastim.
	Pegfilgrastim 6-12 mg/d as a single dose given at least 24 h after completion of chemotherapy and leukapheresis beginning when the peripheral blood stem cell count is adequate	A	52-54	
What type of chemotherapy and dose is recommended for chemomobilization in adult patients?	Disease-specific chemotherapy (IEV, ESHAP, ICE)	C	51-56	Multiple regimens appear to be feasible. Mobilization is generally successful during count recovery after disease-specific chemotherapy.
	Cyclophosphamide	C	55	Greater cell yields mobilization with G-CSF alone and able
	Etoposide	C	56, 57	to collect in fewer apheresis days, but increased risk of hospitalization for neutropenic fever. Higher doses of cyclophosphamide have been used effectively but with more side effects and significantly increased hospitalizations for neutropenic fever.
What is the optimal myeloid growth factor and dose schedule for initial mobilization for *pediatric* patients?	*For growth factor only stem cell mobilization:*			
	Filgrastim 10 μg/kg/day, as a single dose, with leukapheresis beginning on the fifth day	C	58, 59	Few studies are available that compare different dose regimens.
	Plerixafor and filgrastim	C	60	Only case reports are available.
	For chemotherapy combined with growth factor for stem cell mobilization:			
	Filgrastim 5-10 μg/kg/day as a single dose beginning at least 24 h after completion of chemotherapy, with leukapheresis initiated when peripheral blood stem cell count or WBC count adequate or Pegfilgrastim 100 μg/kg, as a single dose, at least 24 h after completion of chemotherapy with leukapheresis beginning when the peripheral blood stem cell count is adequate	C	61-63	Although both are reasonable options, filgrastim is much more commonly used than pegfilgrastim.
What type of chemotherapy and dose is recommended for chemomobilization in *pediatric* patients?	Disease specific chemotherapy	C	61-63	Generally can mobilize with any type of chemotherapy that patients may currently be receiving for treatment of their disease.
What are the target goals for collection from adult and pediatric patients?	Minimum: 2×10^6 $CD34^+$ cells/kg Optimal: 5×10^6 $CD34^+$ cells/kg	B	64, 65	An absolute lower threshold has not been determined, but the generally accepted minimum is 2×10^6 $CD34^+$ cells/kg. For patients with multiple myeloma, a target $CD34^+$ cell dose of greater than 4×10^6 cells/kg is generally accepted (for second transplant).
	Higher number of cells has been associated with improved outcomes	C	66-69	Greater than 8×10^6 $CD34^+$ cells/kg is better, but a direct comparison cannot be made.

(*continued on next page*)

Table 2
(*continued*)

	Recommendation	Strength of Recommendation	References	Comments
When should you begin monitoring peripheral CD34$^+$ counts?	*For growth factors alone:* Beginning on the fourth day of G-CSF *For growth factors and chemotherapy:* Beginning generally 8-10 d after chemotherapy or WBC > 1000/μL. *For growth factors and plerixafor:* The morning before and after plerixafor administration (days 4 and 5 of G-CSF therapy).	C C C	5,70 51-57, 71, 72, 78 48, 49	
When should you initiate leukapheresis?	*For growth factors alone:* Beginning on day +4 or +5 after G-CSF initiation *For growth factors and plerixafor:* Leukapheresis should be initiated the following morning after plerixafor administration. *For growth factors and chemotherapy:* Peripheral CD34$^+$ cell count > 20/μL or if peripheral CD34$^+$ cell count not available, consider when WBC > 5.0 × 10^9/L and platelet count > 75 × 10^9/L	C A C	5, 43-45, 70 48, 49 51-57, 71, 72	Beginning on day +5. A peripheral CD34$^+$ cell count > 20/μL maximizes the likelihood of adequate cell collection with fewer apheresis session. However, in general practice, leukapheresis sometimes initiated at >10/μL. This usually falls 9-12 d after chemotherapy.

engraftment, lower transplant-related mortality, and reduced risk of relapse. However, not all these studies demonstrated an improvement in overall survival because of increased risk of GVHD [25-27]. In the first report, 181 patients with hematologic malignancies received a range of conditioning regimens, and CD34$^+$ cell doses > 8 × 10^6/kg were associated with more rapid neutrophil engraftment but also with development of extensive chronic GVHD. There was no impact on survival, relapse, or acute GVHD [25]. A second study of myeloablative conditioning similarly showed that CD34$^+$ cell doses > 8.3 × 10^6 cells/kg were associated with more frequent extensive chronic GVHD [26]. In the third study by a cooperative group, 253 patients received reduced-intensity conditioning, and total nucleated cell doses > 9.1 × 10^8/kg, rather than higher CD34$^+$ cell dose, were associated with a higher incidence of chronic GVHD, improved leukemia-free survival, and trend toward lower relapse [27]. For matched sibling donor transplants it is important to balance the benefits of faster engraftment with the higher risk for extensive chronic GVHD.

For matched unrelated donor transplants, higher cell doses have not been clearly associated with higher risk of GVHD [28-32]. A study of 932 patients from the NMDP showed that regardless of conditioning regimen intensity, a CD34$^+$ cell dose between 4.5 and 9.5 × 10^6/kg was an independent predictor of improved overall survival. Higher cell doses did not result in greater incidence of acute or chronic GVHD, and CD34$^+$ cell doses above 9.5 × 10^6/kg did not further improve outcomes [29].

Question 4: What are the target CD34$^+$ cell doses for collection and infusion for pediatric patients?

Pediatric-specific data on cell dose optimization is lacking, and clinical practice has mainly been extrapolated from adult data. In the few studies available, higher CD34$^+$ cell doses have been associated with faster engraftment but no impact on overall survival or the risk for developing GVHD [33-36].

Question 5: What type of venous access is recommended?

In several large retrospective reports of adult donor populations, peripheral venous access was adequate for stem cell collection in most patients. However, anywhere from .6% to 20% of donors require central line placement. Line placement was accomplished safely and effectively by interventional radiology [37-41].

Pediatric donors generally require central venous catheter placement. However, in a report from the Pediatric Blood and Marrow Transplant Consortium of 218 collections, 33% of donors between ages 7 and 12 years could be collected with peripheral access. For this reason, younger donors should be carefully evaluated for this possibility. Potential complications from catheter placement using general anesthesia or conscious sedation appear to be limited and mild [19,20].

Autologous Progenitor Cell Transplant

Question 1: What is the optimal myeloid growth factor and dose schedule for initial mobilization for adult patients?

If using growth factors alone, the standard is G-CSF. A daily dose of 10 μg/kg/day, as a single subcutaneous injection, is most commonly used, with leukapheresis beginning on the fifth day [42-44]. No advantage has been shown by split dosing G-CSF [45,46]. There is emerging data on the efficacy of 12 mg pegfilgrastim as a single subcutaneous dose

Table 3
Considerations for Special Populations, Comorbidities, and Other Topics

	Recommendation	Strength of Recommendation	References	Comments
Patients at high risk of stem cell mobilization failure or for remobilization attempt	*High-risk patients:*			
	Upfront use or addition of plerixafor or chemotherapy mobilization during initial mobilization	C	81-88	Many centers have developed algorithms based on risk for stem cell mobilization failure.
	Large-volume leukapheresis	C	89-93	Algorithms need to be based on institutional resources.
	For those who have failed initial mobilization attempt:			
	Plerixafor + growth factors Chemotherapy + growth factors	C	94-97	A rest period of 2-4 wk is recommended before remobilization attempt. Subsequent remobilization can be successful with either addition of plerixafor or chemotherapy plus growth factor. Success rates are much higher with plerixafor plus growth factors.
Pediatric patients with low weight	Patients below 15 kg are generally transfused to achieve hemoglobin $>$ 12 g/dL and platelet count $>$ 40 $\times$ 10^9/L	C	98,99	PBSC harvesting from low-weight patients is safe and effective.
	Priming of the apheresis machine with either RBCs and/or albumin is important for patients who weigh $<$ 20 kg	C	19, 98,99	Priming of the machine compensates for extracorporeal volume and mitigates hemodynamic complications.
	Large volume leukapheresis ($>$3 times total blood volume) can be performed in patients with low birth weight	C	100	
Obese patients	Single daily dosing G-CSF results in improved collection	C	101	Further studies are needed before suggesting a maximum dose of growth factor.
	Increased BMI does not impair ability to collect adequately with plerixafor and G-CSF	C	102	
Should dosing be according to ideal or actual body weight?	Not yet enough data to recommend one approach over the other	C	28, 103	Further studies are warranted; however, if necessary to proceed with transplant, basing cell dose on either may be acceptable.
How to address thrombocytopenia?	*For allogeneic stem cell donors:*			
	Maximum of 2 d of collection and possible transfusion for postapheresis platelet count $<$75 $\times$ 10^9/L.	C	37	Very little data for recommendations
	For autologous stem cell transplant:			
	Transfuse for preapheresis platelet count below 30 $\times$ 10^9/L to prevent bleeding complications.	C	90	
Is there a threshold for leukocytosis for which growth factors should be held?	No recommendation, but general practice for many centers is to withhold G-CSF when WBC $>$ 100 $\times$ 10^9/L and to hold plerixafor when WBC $>$ 75 $\times$ 10^9/L	C	37, 105-109	Theoretical concern is for splenic rupture, but very few data support the recommendations. In case reports where splenic rupture did occur, patients had WBC $>$ 70 $\times$ 10^9/L. However, no study has correlated WBC with risk for splenic rupture. Despite that, G-CSF and plerixafor are typically held at these thresholds.
Are G-CSF biosimilars recommended for use in PBPC mobilization?	Currently, there are insufficient data for recommending the use of G-CSF biosimilars for PBPC mobilization.	C	112-114	

IEV indicates ifosfamide, epirubicin, etoposide; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; ICE, ifosfamide, carboplatin, etoposide.

[47]. However, pegfilgrastim has not been adopted by many centers, likely because of ease and familiarity of use with G-CSF and cost.

The greater effectiveness of plerixafor in combination with G-CSF compared with G-CSF alone was demonstrated in separate randomized studies of patients with lymphoma and myeloma [48,49]. Plerixafor has been approved by the US Food and Drug Administration for use in conjunction with G-CSF for the mobilization of PBPCs for autologous HCT in patients with multiple myeloma and non-Hodgkin lymphoma. Because of its expense, many centers have adopted algorithms favoring pre-emptive addition of plerixafor as a salvage method, and it is uncommonly planned for initial mobilization. For chemotherapy plus growth factor mobilization, G-CSF 5 to 10 μg/kg/day as a single daily dose or pegfilgrastim as a single administration can be used with leukapheresis beginning when peripheral blood $CD34^+$ ($pbCD34^+$) cell count or WBC count is adequate (refer to Question 7 below) [51-57].

Question 2: What type of chemotherapy and dose are recommended for chemomobilization in adult patients?

Chemotherapy-induced mobilization is generally successful during WBC recovery after disease-specific chemotherapy [51-54]. In the absence of specific protocol-driven chemotherapy, cyclophosphamide or etoposide are commonly used for mobilization and result in higher collection yields with fewer days of apheresis than mobilization with growth factor alone. Current data do not support the concern that mobilization regimens that include etoposide promote secondary malignancies [57]. However, these benefits occur at the expense of increased hospitalizations for neutropenic fever, which occur in a substantial portion of patients [55-57].

Question 3: What is the optimal myeloid growth factor and dose schedule for initial mobilization in pediatric patients?

For mobilization with growth factor alone, the most commonly used regimen is daily G-CSF (10 μg/kg/day) with leukapheresis beginning on the fifth day of G-CSF. There is a paucity of data in children regarding dose and scheduling of growth factor alone [58,59]. Sevilla et al. [59] reported that G-CSF 12 μg/kg given twice daily could result in successful 1-day collections. However, side effects appeared to be more frequent than when lower doses were used. More recently, case reports have indicated successful stem cell collections using plerixafor and filgrastim, but existing data are insufficient to provide specific recommendations [60].

For chemotherapy plus growth factor mobilization, both filgrastim and pegfilgrastim have been studied. Although reports indicate similar efficacy and side effect profiles for both, filgrastim is generally used [61-63].

Question 4: What type of chemotherapy and dose are recommended for chemomobilization in pediatric patients?

For children undergoing autologous PBPC collection, mobilization is generally achieved during the marrow recovery phase after disease-specific chemotherapy protocols [62,63].

Question 5: What are the target goals for collection for adult and pediatric patients?

Studies have not demonstrated an absolute threshold cell dose below which hematopoietic recovery will not occur. However, a dose of 2×10^6 $CD34^+$ cells/kg for a single transplant has generally been accepted as a safe minimum. Lower doses have been used, but at the risk of delayed neutrophil and platelet engraftment. Several studies have demonstrated that the optimal number may be greater than 5×10^6 $CD34^+$ cells/kg [64,65]. Higher cell numbers from so-called supermobilizers have been associated with faster hematopoietic recovery, more robust long-term platelet recovery, and improved overall survival [66-69]. In these studies, $CD34^+$ cell doses exceeding 8×10^6 $CD34^+$ cells/kg appeared to be associated with greater benefit. However, these studies are retrospective and have potential bias. Studies are underway to address the question of whether it is the ability to mobilize a higher number of stem cells or the infused CD34 cell dose that is most important.

Question 6: When should you begin monitoring peripheral blood $CD34^+$ cell counts?

Mobilization with G-CSF alone causes $pbCD34^+$ cell counts to peak in the blood between the fourth and sixth days of therapy. For this reason, $pbCD34^+$ cell monitoring should begin on either day 4 or 5 [5,70].

For patients mobilized with chemotherapy and growth factor, $pbCD34^+$ counts generally begin 8 to 10 days after chemotherapy administration, when $CD34^+$ cell counts are expected to peak [51-57,71,72]. Peak timing varies according to the specific chemotherapy regimen used and to patient-specific factors. For patients mobilized with plerixafor plus G-CSF in phase III studies, $pbCD34^+$ cell counts were checked on days 4 and 5 of G-CSF administration (see Table 2) [48,49].

Question 7: When should leukapheresis be initiated?

Leukapheresis is most commonly initiated on day 5 when mobilization is achieved with G-CSF alone or G-CSF plus plerixafor [5,43-45,70]. When mobilization is achieved with chemotherapy, the start of leukapheresis is commonly determined by a threshold $pbCD34^+$ cell count. There is no consensus on the optimal threshold, and institutional practice has varied from a minimal $pbCD34^+$ count of 5 to 20/μL. One retrospective study of 95 patients found that a minimal $pbCD34^+$ cell count of 5 cells/μL was adequate to meet a specified collection goal; however, that goal of $.75 \times 10^6$ or 1.25×10^6 $CD34^+$ cells/kg is considered to be low [70]. Another study of 48 patients suggested that a $pbCD34^+$ cell count of at least 15 cells/μL was adequate when the collection goal was only 1.5×10^6 $CD34^+$ cells/kg [71]. A more common target collection goal is at least 2×10^6 $CD34^+$ cells/kg, and Elliot et al. [72] reported that more than 90% of 39 study patients achieved this goal when the threshold $pbCD34^+$ cell count for starting leukapheresis exceeded 20 cells/μL.

Considerations for Special Populations, Comorbidities, and Other Topics

Question 1: What are possible ways to identify and address patients at high risk for stem cell mobilization failure?

What is the preferred agent for remobilization attempt? Gertz et al. [73] reported on 1775 patients who were mobilized over a 7-year period. Patients were classified according to $CD34^+$ cell yield: optimal collection ($\geq 5 \times 10^6$ $CD34^+$ cells/kg), low collection (≥ 2 to $< 5 \times 10^6$ $CD34^+$ cells/kg), poor collection ($< 2 \times 10^6$ $CD34^+$ cells/kg), and failed collection (apheresis not attempted because of low peripheral $pbCD34^+$ cell count). Less than optimal collections were observed for 47% of patients, among whom 37% proceeded to transplant and the other 63% went on to further mobilization attempts. With subsequent attempts, there was increased use of growth factor support, antibiotic use, and transfusions,

emphasizing the extensive resource utilization associated with stem cell mobilization failures [73].

Multiple studies have analyzed poor mobilizers and have identified age greater than 60 years, multiple chemotherapy regimens, prior exposure to alkylating therapy or prior radiation, prior treatment with lenalidomide, and platelet count below 100×10^9/L [65,73-76]. Once mobilization has begun, other factors include low pbCD34$^+$ cell count and poor collection on day 1 [77,78]. Therefore, many programs have developed algorithms to identify high-risk populations and to initiate rescue therapy during the first mobilization attempt to increase the likelihood of success [77-87]. The practice of escalating G-CSF doses to 20 to 30 μk/kg/day, when patients are not ready for collection 12 or 13 days after chemotherapy plus G-CSF at 10 μg/kg/day, is expensive and generally unsubstantiated. Similarly, data are insufficient in this scenario to support a day 12 or 13 rescue dose of plerixafor [88,89]. These risk-adapted strategies have not yet been validated, and further studies are needed.

Another strategy that has improved cell collection yield is large-volume leukapheresis [90-94]. For patients who fail an initial mobilization attempt, a rest period of 2 to 4 weeks is generally recommended before a subsequent attempt. Growth factors alone are generally not successful. Even combination growth factor support results in failure rates in excess of 80%. Chemotherapy with growth factor support also results in higher than desired failure rates and with more toxicities [95]. Plerixafor plus G-CSF (without chemotherapy) results in the highest success when used in the standard manner and is the preferred approach [96,97].

Question 2: How do you address pediatric patients with low weight?

One of the main concerns regarding pediatric patients with low body weight is the associated low blood volume. A low extracorporeal volume is necessary to mitigate hemodynamic complications. Patients of low weight should have hemoglobin of at least 12 g/dL or should be transfused with RBCs to reach this level [98]. Similarly, when severe thrombocytopenia is present, platelet transfusion to above 40×10^9/L is recommended to prevent bleeding complications. In children who weigh less than 20 kg, the apheresis machine should be primed with RBCs and/or human albumin to lower the extracorporeal volume [19,99].

Question 3: Are there special considerations for obese patients?

There are little data to address growth factor dosing in obese patients. One retrospective study of 86 patients reviewed outcomes after 2 different G-CSF mobilization regimens: either single daily dose (14 μg/kg/day) or split dose (2×7 μg/kg/day). Patients were stratified according to body mass index (BMI; $\leq$25 or $>$25). In patients with BMI > 25 kg/m^2, once-daily dosing resulted in a higher CD34$^+$ cell yield [101]. Another retrospective study of 356 patients found that BMI $\geq$ 25 did not affect the CD34$^+$ cell yields when mobilization was achieved by plerixafor plus G-CSF. Although not statistically significant, there was a trend that patients with higher BMI required more apheresis sessions and a higher total dose of plerixafor, but this could possibly be overcome if plerixafor dose and/or CD34$^+$ dose were according to ideal and not actual body weight [102].

Waples et al. [103] performed a retrospective analysis comparing PBPC dosing by ideal versus actual body weight. In 63 patients who underwent progenitor cell mobilization with chemotherapy and G-CSF, 49% were greater than 25% over their ideal body weight. In this study, higher cell doses were associated with improved hematopoietic recovery, regardless of whether ideal or actual body weight calculation were used. Also, 16% of patients would have had 1 less apheresis procedure performed if ideal weight were used. More recently, Pulsipher et al. [29] also reported that similar outcomes in adult patients whether CD34$^+$ cell dose was based on actual or ideal body weight. Although other unpublished NMDP data also suggest that dosing obese patients according to ideal body weight might be sufficient, additional studies are needed before this becomes a recommended standard practice [103]. Further evaluation of effects on G-CSF, CD34$^+$ cell dosing, and body weight may be of increasing importance as a cost-saving measure.

Question 4: How do you manage thrombocytopenia?

Leukapheresis procedures usually result in a decrease in platelet count. Although some variability may exist in the extent of platelet loss depending on the type of apheresis machine, this occurs because of an inability to completely separate platelets from the target cell layer in the centrifuge. This, coupled along with the anticoagulants necessary for the extracorporeal circuit, may increase bleeding risk in patients who begin their collection with thrombocytopenia [90].

For allogeneic donors, safety is of primary concern. Among 2408 unrelated donors from the NMDP, after 2 days of collection nearly 40% had platelet counts below 100×10^9/L and 2% had platelet counts below 50×10^9/L (with a single donor having a platelet count below 20×10^9/L) [37]. The NMDP recommends that unrelated donors not undergo leukapheresis for more than 2 days. Furthermore, the safety of continuing leukapheresis must be carefully considered if the platelet count falls below $<100 \times 10^9$/L [104]. Similar standards should be considered for adult related donors.

Question 5: Is there is a threshold of leukocytosis for which growth factor should be held?

There are minimal data to guide the management of mobilization in patients who have leukocytosis. The risk of growth factor–induced splenic rupture is an important concern. In the report on 2408 donors from the NMDP, nearly a third developed WBC blood counts exceeding 50×10^9/L, but fewer than 1% had WBC counts exceeding 75×10^9/L. There was no splenic rupture or thrombosis [37].

However, several isolated case reports describe donors who had splenic rupture in whom WBC counts at the time of the event exceeded 50×10^9/L [105-107]. In a report on 91 donors that assessed splenic size by ultrasound and palpation during G-CSF mobilization, a significant increase in spleen size was observed, but there was no correlation with any hematologic parameters and no splenic complications [108]. More recently, Stiff et al. [109] reported on 306 donors undergoing G-CSF mobilization and splenic assessments performed by ultrasound and physical exam. The median spleen volume increased by 1.47-fold on the first day of leukapheresis but declined to near pretreatment size by 7 days after leukapheresis. In only 9% of patients did splenic volumes increase by more than 2-fold. There were no splenic ruptures. There was no correlation between change in spleen volume, G-CSF dose, peak absolute neutrophil count, CD34$^+$ cell yield, or donor weight [109]. Despite the lack of association between hematologic parameters and splenic enlargement or risk of splenic rupture, the general practice is to withhold G-CSF when the WBC count exceeds 100×10^9/L

and to withhold plerixafor when the WBC count exceeds 75×10^9/L.

Question 6: Are G-CSF biosimilars recommended for use in PBPC mobilization?

Approved biosimilar G-CSFs are produced and manufactured by a similar process to the innovator (original) biologic and generally sold at lower prices. Data support their role in chemotherapy-induced neutropenia with cost efficiency [110,111]; however, less data are available regarding their use in PBSC mobilization [112-114]. Lefrere et al. [112] reported on their first experience in 40 patients undergoing mobilization with biosimilar G-CSF. Compared with a historical cohort group treated with G-CSF, there were no significant differences in median $CD34^+$ cell collection. Schmitt et al. [113] recently reported comparable efficacy and safety in 22 healthy donors using a G-CSF biosimilar XM02 compared with G-CSF. In another retrospective, single-institution study of 96 patients comparing filgrastim, biosimilar filgrastim, and lenograstim, biosimilar filgrastim was found to be comparable with filgrastim for collection yields [114]. Larger controlled studies with longer term follow-up are necessary before recommending the use of these agents for mobilization.

CONCLUSIONS

Hematopoietic progenitor cell mobilization and collection is an evolving area with wide variation in clinical practice. Although each institution varies according to patient demographics, financial limitations, and resource availability, the American Society for Blood and Marrow Transplantation Practice Guidelines Subcommittee developed this "frequently asked question" style review with the goal to provide transplant practitioners with straightforward consensus and evidence-driven practice guidelines.

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REFERENCES

1. Giralt S, Costa L, Scriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. *Biol Blood Marrow Transplant*. 2014; 20:295-308.
2. Jones R, Nnieto Y, Rizzo JD, et al. The evolution of the evidence-based review: evaluating the science enhances the art of medicine—statement of the Steering Committee for Evidence-Based Reviews of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2005;11:819-822.
3. Fischmeister G, Kurz M, Haas OA. G-CSF versus GM-CSF for stimulation of peripheral blood progenitor cells (PBPC) and leukocytes in healthy volunteers: comparison of efficacy and tolerability. *Ann Hematol*. 1999;78:117-123.
4. Sohn SK, Kim JG, Seao KW, et al. GM-CSF-based mobilization effect in normal healthy donors for allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2002;30:81-86.
5. Grigg AP, Roberts AW, Raunow H, et al. Optimizing dose and scheduling of filgrastim (granulocyte colony-stimulating factor) for mobilization and collection of peripheral blood progenitor cells in normal volunteers. *Blood*. 1995;86:4437-4445.
6. Schmitz N, Bacigalupo A, Hasenclever D, et al. Allogeneic bone marrow transplantation vs. filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomized multi-center trial of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 1998;21:995-1003.
7. Engelhardt M, Bertz H, Afting M, et al. High-versus standard-dose filgrastim (rhG-CSF) for mobilization of peripheral-blood progenitor cells from allogeneic donors and CD34(+) immunoselection. *J Clin Oncol*. 1999;17:2160-2172.
8. Kroger N, Renges H, Sonnenberg S, et al. Stem cell mobilization with 16 microg/kg vs 10 microg/kg of G-CSF for allogeneic transplantation in healthy donors. *Bone Marrow Transplant*. 2002;29:727-730.
9. Kroger N, Renges H, Kruger W, et al. A randomized comparison of once versus twice daily r-Hu granulocyte colony-stimulating factor (filgrastim) for stem cell mobilization in healthy donors for allogeneic transplantation. *Br J Haematol*. 2000;111:761-765.
10. Anderlini P, Donato M, Chan KW, et al. Allogeneic blood progenitor cell collection in normal donors after mobilization with filgrastim: the M.D. Anderson Cancer Center experience. *Transfusion*. 1999;39:555-560.
11. Lane TA, Law P, Maruyama M, et al. Harvesting and enrichment of hematopoietic progenitor cells mobilized into the peripheral blood of normal donors by granulocyte-macrophage colony-stimulating factor (GM-CSF) or G-CSF: potential role in allogeneic marrow transplantation. *Blood*. 1995;85:275-282.
12. Kim SN, Moon JH, Kim JG, et al. Mobilization effects of G-CSF, GM-CSF, and darbepoietin-alpha for allogeneic peripheral blood stem cell mobilization. *J Clin Apher*. 2009;24:173-179.
13. Lonial S, Akhtari M, Kaufman J, et al. Mobilization of hematopoietic progenitors from normal donors using the combination of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor results in few plasmacytoid dendritic cells in the graft and enhanced donor T-cell engraftment with Th1 polarization: results from a randomized clinical trial. *Biol Blood Marrow Transplant*. 2013;19:460-467.
14. Ings SJ, Balsa C, Leverett D, et al. Peripheral blood stem cell yield in 400 normal donors mobilized with granulocyte colony-stimulating factor (G-CSF): impact of age, sex, donor weight and type of G-CSF used. *Br J Haematol*. 2006;134:517-525.
15. Perez-Lopez O, Martin-Sanchez J, Parody-Porras R, et al. Lenograstim compared to filgrastim for the mobilization of hematopoietic stem cells in healthy donors. *Transfusion*. 2013;53:3240-3242.
16. Hill GR, Morris ES, Fuery M, et al. Allogeneic stem cell transplantation with peripheral blood stem cells mobilized by pegylated G-CSF. *Biol Blood Marrow Transplant*. 2006;12:603-607.
17. Kroschinsky F, Holig K, Poppe-Thiede K, et al. Single-dose pegfilgrastim for the mobilization of allogeneic CD34+ peripheral blood progenitor cells in healthy family and unrelated donors. *Haematologica*. 2005;90:1665-1671.
18. Devine SM, Vij R, Rettig M, et al. Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of CXCR4/SDF-1 interaction. *Blood*. 2008;112:990-998.
19. Pulsipher MA, Levine JE, Hayashi RJ. Safety and efficacy of allogeneic PBSC collection in normal pediatric donors: The Pediatric Blood and Marrow Transplant Consortium Experience (PBMTC) 1996-2003. *Bone Marrow Transplant*. 2005;35:361-367.
20. Styczynski J, Balduzzi A, Gil L, et al. Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective EBMT-PDWP study. *Blood*. 2012;119:2935-2942.
21. Kawano Y, Takaue Y, Watanabe T, et al. Efficacy of the mobilization of peripheral blood stem cells by granulocyte colony-stimulating factor in pediatric donors. *Cancer Res*. 1999;59:3321-3324.
22. Diaz MA, Sevilla J, de la Rubia J, et al. Factors predicting peripheral blood progenitor cell collection from pediatric donors for allogeneic transplantation. *Haematologica*. 2003;88:919-922.
23. Sevilla J, Gonzelz-Vicent M, Lassaletta A, et al. Peripheral blood progenitor cell collection adverse events for childhood allogeneic donors: variables related to the collection and safety profile. *Br J Haematol*. 2009;144:909-916.
24. Perez-Simon JA, Diez Campelo M, Martino R, et al. Impact of CD34+ cell dose on the outcome of patients undergoing reduced-intensity-conditioning allogeneic peripheral blood stem cell transplantation. *Blood*. 2003;102:1108-1113.
25. Zaucha JM, Gooley T, Bensinger WI, et al. CD34+ cell dose in granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell graft affects engraftment kinetics and development of extensive chronic graft-versus-host disease after HLA-identical sibling transplantation. *Blood*. 2001;98:3221-3227.
26. Mohty M, Bilger K, Jourdan E, et al. Higher doses of CD34+ peripheral blood stem cells are associated with increased mortality from chronic graft-versus-host disease after allogeneic HLA-identical sibling transplantation. *Leukemia*. 2003;17:869-875.
27. Gorin NC, Labopin M, Boiron JM, et al. Results of genoidentical hemopoietic stem cell transplantation with reduced intensity

conditioning for acute myelocytic leukemia: higher dose of stem cells infused benefit patients receiving transplants in second remission or beyond—the Acute Leukemia Working Part of the European Cooperative Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2006;24:3959-3966.
28. Nakamura R, Nademanee A, Smith DD, et al. Impact of graft cell dose on transplant outcomes following unrelated donor allogeneic peripheral blood stem cell transplantation: higher CD34+ cell doses are associated with decreased relapse rates. *Biol Blood Marrow Transplant*. 2008;14:449-457.
29. Pulsipher MA, Chitphakdithai P, Logan BR, et al. Donor, recipient and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34+ cell dose. *Blood*. 2009;114:2606-2616.
30. Mehta J, Frankfurt O, Altman J, et al. Optimizing the CD34+ cell dose for reduced-intensity allogeneic hematopoietic stem cell transplantation. *Leuk Lymph*. 2009;50:1434-1441.
31. Holtan SG, Hogan WF, Elliott MA, et al. CD34+ cell dose and establishment of full donor chimerism at day +100 are important factors for survival with reduced-intensity conditioning with fludarabine and melphalan before allogeneic hematopoietic SCT for hematologic malignancies. *Bone Marrow Transplant*. 2010;45:1699-1703.
32. Islam MS, Anoop P, Datta-Nemdharry P, et al. Implications of CD34+ cell dose on clinical and haematological outcome of alloHSCT for acquired aplastic anemia. *Bone Marrow Transplant*. 2010;45:886-894.
33. Chiang KY, Haight A, Horan J, et al. Clinical outcomes and graft characteristics in pediatric matched sibling donor transplants using granuloycte colony-stimulating factor-primed bone marrow and steady-state bone marrow. *Pediatr Transplant*. 2007;11:279-285.
34. Kalwak K, Porwolik J, Mielcarek M, et al. Higher CD34(+) and CD3(+) cell doses in the graft promote long-term survival, and have no impact on the incidence of severe acute or chronic graft-versus-host disease after in vivo T-cell depleted unrelated donor hematopoietic stem cell transplantation in children. *Biol Blood Marrow Transplant*. 2010;16:1388-1401.
35. Chang YJ, Xu LP, Liu DH, et al. The impact of CD34+ cell dose on platelet engraftment in pediatric patients following unmanipulated haploidentical blood and marrow transplantation. *Pediatr Blood Cancer*. 2009;53:1100-1106.
36. Liu DH, Zhao XS, Chang YJ, et al. The impact of graft composition on clinical outcomes in pediatric patients undergoing unmanipulated HLA-mismatched/haploidentical hematopoietic stem cell transplantation. *Pediatr Blood Cancer*. 2011;57:135-141.
37. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2009;113:3604-3611.
38. Holig K, Kramer M, Kroschinsky F, et al. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. *Blood*. 2009;114:3757-3763.
39. Al-Ali HK, Bourgeois M, Krahl R, et al. The impact of the age of HLA-identical siblings on mobilization and collection of PBSCs for allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2011;46:1296-1302.
40. Wang TF, Wen SH, Chen RL, et al. Factors associated with peripheral blood stem cell yield in volunteer donors mobilized with granulocyte colony-stimulating factors: the impact of donor characteristics and procedural settings. *Biol Blood Marrow Transplant*. 2008;14:1305-1311.
41. Sadler DJ, McCarthy M, Saliken JC, et al. Image-guided central venous catheter placement for apheresis in allogeneic stem cell donors. *J Clin Apher*. 2000;15:173-175.
42. Schmitz N, Linch DC, Dreger P, et al. Randomized trial of filgrastim-mobilized peripheral blood progenitor cell transplantation versus autologous bone marrow transplantation in lymphoma patients. *Lancet*. 1996;347:353-357.
43. Peters WP, Rosner G, Ross M, et al. Comparative effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. *Blood*. 1993;81:1709-1719.
44. Spitzer G, Adkins D, Mathews M, et al. Randomized comparison of G-CSF + GM-CSF vs. G-CSF alone for mobilization of peripheral blood stem cells: effects on hematopoietic recovery after high-dose chemotherapy. *Bone Marrow Transplant*. 1997;20:921-930.
45. Carrion R, Serrano D, Gomez-Pineda A, et al. A randomized study of 10μg/kg/day (single dose) vs 2 × 5 μg/kg/day (split dose) G-CSF as stem cell mobilization regimen in high risk breast cancer patients. *Bone Marrow Transplant*. 2003;32:563-567.
46. Kim S, Kim HJ, Park JS, et al. Prospective randomized comparative observation of single- vs. split-dose lenograstim to mobilize peripheral blood progenitor cells following chemotherapy in patients with multiple myeloma or non-Hodgkin's lymphoma. *Ann Hematol*. 2005;84:742-747.
47. Herbert KE, Gambell P, Link EK, et al. Pegfilgrastim compared with filgrastim for cytokine-alone mobilization of autologous haematopoietic stem and progenitor cells. *BMT*. 2013;48:351-356.
48. DiPersio JF, Micallef IN, Stiff PJ, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27:4767-4773.
49. DiPersio JF, Stadtmaur EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoetic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood*. 2009;113:5720-5726.
50. Cooper DL, Pratt K, Baker J, et al. Late afternoon dosing of plerixafor for stem cell mobilization: a practical solution. *Clin Lymph Myel Leuk*. 2011;11:267-272.
51. Weaver CH, Schulman KA, Wilson-Relyea B, et al. Randomized trial of filgrastim, sargramostim, or sequential sargramostim and filgrastim after myelosuppressive chemotherapy for the harvesting of peripheral blood stem cells. *J Clin Oncol*. 2000;18:43-53.
52. Isidori A, Tani M, Bonifazi F. Phase II study of single pegfilgrastim injection as an adjunct to chemotherapy to mobilize stem cells into the peripheral blood of pretreated lymphoma patients. *Haematologica*. 2005;90:225-231.
53. Simona B, Cristina R, Luca N, et al. A single dose of pegfilgrastim versus daily filgrastim to evaluate the mobilization and the engraftment of autologous peripheral hematopoietic progenitors in malignant lymphoma patients candidate for high-dose chemotherapy. *Trans Apher Sci*. 2010;43:321-326.
54. Russell N, Mesters R, Schubert J, et al. A phase 2 pilot study of pegfilgrastim and filgrastim for mobilizing peripheral blood progenitor cells in patients with non-Hodgkin's lymphoma receiving chemotherapy. *Haematologica*. 2008;93:405-412.
55. Hamadani M, Kochuparambil ST, Osman S, et al. Intermediate-dose versus low-dose cyclophosphamide and granulocyte colony-stimulating factor for peripheral blood stem cell mobilization in patients with multiple myeloma treated with novel induction therapies. *Biol Blood Marrow Transplant*. 2012;18:1128-1135.
56. Wood WA, Whitley J, Moore D, et al. Chemomobilization with etoposide is highly effective in patients with multiple myeloma and overcomes the effects of age and prior therapy. *Biol Blood Marrow Transplant*. 2011;17:141-146.
57. Mahindra A, Bolwell BJ, Rybicki L, et al. Etoposide plus G-CSF priming compared with G-CSF alone in patients with lymphoma improves mobilization without an increased risk of secondary myelodysplasia and leukemia. *Bone Marrow Transplant*. 2012;47:231-235.
58. Watanabe H, Watanabe T, Suzuya H, et al. Peripheral blood stem cell mobilization by granulocyte colony-stimulating factor alone and engraftment kinetics following autologous transplantation in children and adolescents with solid tumor. *Bone Marrow Transplant*. 2006;37:661-668.
59. Sevilla J, Gonzalez-Vicent M, Madero L, et al. Granulocyte colony-stimulating factor alone at 12mcg/kg twice a day for 4 days for peripheral blood progenitor cell priming in pediatric patients. *BMT*. 2002;30:417-420.
60. Vettenranta K, Mottonen M, Riikonen P. The use of plerixafor in harvesting autologous stem cells in the pediatric setting. *Pediatr Blood Cancer*. 2012;59:197-198.
61. Cesaro S, Zanazzo AG, Frenos S, et al. A Phase II study on the safety and efficacy of a single dose of pegfilgrastim for mobilization and transplantation of autologous hematopoietic stem cells in pediatric oncohematology patients. *Transfusion*. 2011;51:2480-2487.
62. Fritsch P, Schwinger W, Schwantzer G, et al. Peripheral blood stem cell mobilization with pegfilgrastim compared to filgrastim in children and young adults with malignancies. *Pediatr Blood Cancer*. 2010;54:134-137.
63. Fox E, Widemann BC, Hawkins DS, et al. Randomized trial and pharmacokinetic study of pegfilgrastim versus filgrastim after dose-intensive chemotherapy in young adults and children with sarcomas. *Clin Cancer Res*. 2009;15:7361-7367.
64. Weaver CH, Hazelton B, Birch R, et al. An analysis of engraftment kinetics as a function of the CD34 content of peripheral blood progenitor cell collection in 692 patients after the administration of myeloablative chemotherapy. *Blood*. 1995;86:3961-3969.
65. Bensinger W, Appelbaum F, Rowley S, et al. Factors that influence collection and engraftment of autologous peripheral blood stem cells. *J Clin Oncol*. 1995;13:2547-2555.
66. Bolwell BJ, Pohlman B, Rybicki L, et al. Patients mobilizing large numbers of CD34+ cells ("super mobilizers") have improved survival in autologous stem cell transplantation for lymphoid malignancies. *Bone Marrow Transplant*. 2007;40:437-441.
67. Yoon DH, Sohn BS, Jang G, et al. Higher infused CD34+ hematopoietic stem cell dose correlates with earlier lymphocyte recovery and better clinical outcome after autologous stem cell transplantation in non-Hodgkin's lymphoma. *Transfusion*. 2009;49:1890-1900.

68. Ketterer N, Salles G, Raba M, et al. High CD34+ cell counts decrease hematologic toxicity of autologous peripheral blood progenitor cell transplantation. *Blood*. 1998;91:3148-3155.
69. Stiff PJ, Micallef I, Nademanee AP, et al. Transplanted CD34(+) cell dose is associated with long-term platelet count recovery following autologous peripheral blood stem cell transplant in patients with non-Hodgkin lymphoma or multiple myeloma. *Biol Blood Marrow Transplant*. 2011;17:1146-1153.
70. Perez-Simon JA, Corral CM, Nieto MJ, et al. Minimal number of circulating CD34+ cells to ensure successful leukapheresis and engraftment in autologous peripheral blood progenitor cell transplantation. *Transfusion*. 1998;38:385-391.
71. Basquiera AL, Abichain P, Damonte JC, et al. The number of CD34+ cells in peripheral blood as a predictor of the CD34+ yield in patients going to autologous stem cell transplantation. *J Clin Apher*. 2006;21:92-95.
72. Elliott C, Samson DM, Armitage S, et al. When to harvest peripheral-blood stem cells after mobilization therapy: prediction of CD34-positive cell yield by preceding day CD34-positive concentration in peripheral blood. *J Clin Oncol*. 1996;14:970-973.
73. Gertz MA, Wolf RC, Micallef IN, et al. Clinical impact and resource utilization after stem cell mobilization failure in patients with multiple myeloma and lymphoma. *Bone Marrow Transplant*. 2010;45:1396-1403.
74. Hosing C, Saliba RM, Ahlawat S, et al. Poor hematopoietic stem cell mobilizers: a single institution study of incidence and risk factors in patients with recurrent or elapsed lymphoma. *Am J Hematol*. 2009;84:335-337.
75. Clark RE, Brammer CG. Previous treatment predicts the efficiency of blood progenitor cell mobilization: validation of a chemotherapy scoring system. *Bone Marrow Transplant*. 1998;22:859-863.
76. Popat U, Saliba R, Thandi R, et al. Impairment of filgrastim-induced stem cell mobilization after prior lenalidomide in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2009;15:718-723.
77. Sinha S, Gastineau D, Micallef I, et al. Predicting PBSC harvest failure using circulating CD34 levels: developing target-based cutoff points for early intervention. *Bone Marrow Transplant*. 2011;46:943-949.
78. Yu J, Leisenring W, Bensinger WI, et al. The predictive value of white cell or CD34+ cell count in the peripheral blood for timing apheresis and maximizing yield. *Transfusion*. 1999;39:442-450.
79. Rujkijyanont P, Hipps J, Gan K, et al. Prediction of CD34+ cell yield in hematopoietic cell products from children by peripheral blood CD34+ cell counts. *Cytotherapy*. 2012;14:472-482.
80. Callera F, Cavenaghi L, De Melo CM. Peripheral blood progenitor cell collection without close monitoring of peripheral blood CD34+ cells: a feasible strategy for multiple myeloma or pre-treated non-Hodgkin's lymphoma patients mobilized with low-dose cyclophosphamide plus G-CSF. *Transfus Apher Sci*. 2009;40:91-95.
81. Jantunen E, Varmavuo V, Juutilainen A, et al. Kinetics of blood CD34+ cells after chemotherapy plus G-CSF in poor mobilizers: Implications for pre-emptive plerixafor use. *Ann Hematol*. 2012;91:1073-1079.
82. Ozsan GH, Micallef IN, Dispenzieri A, et al. Hematopoietic recovery kinetics predicts for poor CD34+ cell mobilization after cyclophosphamide chemotherapy in multiple myeloma. *Am J Hematol*. 2012;87:1-4.
83. Malard F, Kroger N, Gabriel IH, et al. Plerixafor for autologous peripheral blood stem cell mobilization in patients previously treated with fludarabine or lenalidomide. *Biol Blood Marrow Transplant*. 2012;18:314-317.
84. Maziarz RT, Nademanee AP, Micaellef IN, et al. Plerixafor plus granulocyte colony-stimulating factor improves the mobilization of hematopoietic stem cells in patients with non-Hodgkin lymphoma and low-circulating peripheral blood CD34+ cells. *Biol Blood Marrow Transplant*. 2013;19:661-675.
85. Li J, Hamilton E, Vaughn L, et al. Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics. *Transfusion*. 2011;51:2175-2182.
86. Costa LJ, Kramer C, Hogan KR, et al. Pegfilgrastim- versus filgrastim-based autologous hematopoietic stem cell mobilization in the setting of preemptive use of plerixafor: efficacy and cost analysis. *Transfusion*. 2012;52:2375-2381.
87. Mark T, Stern J, Furst JR, et al. Stem cell mobilization with cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in multiple myeloma. *Biol Blood Marrow Transplant*. 2008;14:795-798.
88. Jantunen E, Kuittinen T, Mahlamaki E, et al. Efficacy of pre-emptively used plerixafor in patients mobilizing poorly after chemomobilization: a single center experience. *Eur J Haematol*. 2011;86:299-304.
89. Milone G, Martino M, Spadaro A, et al. Plerixafor on-demand combined with chemotherapy and granulocyte colony-stimulating factor: significant improvement in peripheral blood stem cells mobilization and harvest with no increase in costs. *Br J Haematol*. 2014;164:113-123.
90. Sarcodee-Adoo C, Taran I, Guo C, et al. Influence of preapheresis clinical factors on the efficiency of CD34+ cell collection by large-volume apheresis. *Bone Marrow Transplant*. 2003;31:851-855.
91. Gasova Z, Marinov I, Vodvarkova S, et al. PBPC collection techniques: standard versus large volume leukapheresis (LVL) in donors and patients. *Trans Apher Sci*. 2005;32:167-176.
92. Majado MJ, Minguela A, Gonzalez-Garcia C, et al. Large-volume-apheresis facilitates autologous transplantation of hematopoeitic progenitors in poor mobilizer patients. *J Clin Apher*. 2009;24:12-17.
93. Bojanic I, Dubravcic K, Batinic D, et al. Large volume leukapheresis: efficacy and safety of processing patient's total blood volume six times. *Transfus Apher Sci*. 2011;44:139-147.
94. Diaz MA, Garcia-Sanchez F, Lillo R, et al. Large-volume leukapheresis in pediatric patients: pre-apheresis peripheral blood CD34+ cell count predicts progenitor cell yield. *Haematologica*. 1999;84:32-35.
95. Pusic I, Jiang SY, Landua S, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. *Biol Blood Marrow Transplant*. 2008;3:687-694.
96. Calandra G, McCarty J, McGuirk J, et al. AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma patients, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: compassionate use data. *Bone Marrow Transplant*. 2008;41:331-338.
97. Duarte RF, Shaw BE, Marin P, et al. Plerixafor plus granulocyte CSF can mobilize hematopoietic stem cells from multiple myeloma and lymphoma patients failing previous mobilization attempts: EU compassionate use dat. *Bone Marrow Transplant*. 2011;46:52-58.
98. Orbach D, Hojjat-Assari S, Doz F, et al. Peripheral blood stem cell collection in 24 low-weight infants: experience of a single centre. *Bone Marrow Transplant*. 2003;31:171-174.
99. Takaue Y, Kawano Y, Abe T, et al. Collection and transplantation of peripheral blood stem cells in very small children weighting 20 kg or less. *Blood*. 1995;86:372-380.
100. Cecyn KZ, Seber A, Ginani VC, et al. Large-volume leukapheresis for peripheral blood progenitor cell collection in low body weight pediatric patients: a single center experience. *Transfus Apher Sci*. 2005;32:269-274.
101. Cetin T, Arpaci F, Ozet A, et al. Stem cell mobilization by G-CSF in solid and hematological malignancies: single daily dose is better than split dose in obese patients. *J Clin Apher*. 2003;18:120-124.
102. Basak GW, Wiktor-Jedrzejczak W, Apperley JF, et al. Higher BMI is not a barrier to stem cell mobilization with standard doses of plerixafor and G-CSF. *Bone Marrow Transplant*. 2012;47:1003-1005.
103. Waples JM, Moreb JS, Sugrue M, et al. Comparison of autologous peripheral blood stem cell dosing by ideal vs actual body weight. *Bone Marrow Transplant*. 1999;23:867-873.
104. Miller J. Filgrastim-mobilized peripheral blood stem cells for allogeneic transplantation with unrelated donors. A protocol of the National Marrow Donor Program. Copyright © 1999-2009 National Marrow Donor Program. Available at: http://bethematch.org/.
105. Dincer AP, Gottschall J, Margolis DA, et al. Splenic rupture in a parental donor undergoing peripheral blood progenitor cell mobilization. *J Pediatr Hematol Oncol*. 2004;26:761-763.
106. Falzetti F, Aversa F, Minelli O, et al. A spontaneous rupture of spleen during peripheral blood stem cell mobilization in a healthy donor [letter]. *Lancet*. 1999;353:555.
107. Nuamah NM, Goker H, Kilic YA, et al. Spontaneous splenic rupture in a healthy allogeneic donor of peripheral-blood stem cell following the administration of granulocyte colony-stimulating factor (G-CSF). A case report and review of the literature. *Haematologica*. 2006;91:ECR08.
108. Platzbecker U, Prange-Krex G, Bornhauser M, et al. Spleen enlargement in healthy donors during G-CSF mobilization of PBPCs. *Transfusion*. 2001;41:184-189.
109. Stiff PJ, Bensinger W, Abidi MH, et al. Clinical and ultrasonic evaluation of spleen size during peripheral blood progenitor cell mobilization by filgrastim: results of an open-label trial in normal donors. *Biol Blood Marrow Transplant*. 2009;15:827-834.
110. Waller CF, Semiglazov VF, Tjulandin S, et al. A phase III randomized equivalence study of biosimilar filgrastim versus Amgen filgrastim in patients receiving myelosuppressive chemotherapy for breast cancer. *Onkologie*. 2010;33:504-511.
111. Engert A, Griskevicius L, Zyuzgin Y, et al. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. *Leuk Lymph*. 2009;50:374-379.
112. Lefrere F, Brignier AC, Elie C, et al. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. *Adv Ther*. 2011;28:301-310.
113. Schmitt M, Xu X, Schneider C, et al. Mobilization of PBSC for allogeneic transplantation by the use of the G-CSF biosimilar XM02 in healthy donors. *Bone Marrow Transplant*. 2013;48:922-925.
114. Sivgin S, Karakus E, Kaynar L, et al. The comparison of filgrastim (Neupogen®), biosimilar filgrastim (Leucostim®) and lenograstim (Granocyte®) as a first line peripheral blood stem cell mobilization strategy in autologous hematopoietic stem cell transplantation: A single center experience from Turkey. *Transf Apher Sci*. 2013;48:315-320.

GRADING SYSTEM FOR RANKING RECOMMENDATIONS IN CLINICAL GUIDELINES [1]

Levels of Evidence

- 1++ High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2++ High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
- 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
- 2- Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
- 3 Nonanalytic studies, eg, case reports or case series
- 4 Expert opinion

Grades of Recommendation

- A At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
- B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
- C A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
- D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

RCT indicates randomized clinical trial.