

Use of Plerixafor for Stem Cell Mobilization in the Setting of Autologous and Allogeneic Stem Cell Transplantations: An Update

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Abstract: Mobilization failure is an important issue in stem cell transplantations. Stem cells are yielded from the peripheral blood via apheresis. Granulocyte colony-stimulating factor (G-CSF) is the most commonly used mobilization agent among patients and donors. G-CSF is administered subcutaneously for multiple days. However, patients with mobilization failure cannot receive autologous stem cell transplantation and, therefore, cannot be treated adequately. The incidence rate of mobilization failure among patients is about 6–23%. Plerixafor is a molecule that inhibits the binding of chemokine receptor-4 with stromal-cell-derived factor-1, thereby resulting in the release of CD34+ cells in the peripheral blood. Currently, plerixafor is used in patients with mobilization failure with G-CSF and is administered subcutaneously. Several studies conducted on different clinical settings have shown that plerixafor is effective and well tolerated by patients. However, more studies should be conducted to explore the optimal approach for plerixafor in patients with mobilization failure. The incidence of mobilization failure among donors is lower. However, plerixafor is not approved among donors with mobilization failure. Moreover, several clinical studies in donors have shown a beneficial effect of plerixafor. In addition, the adverse events of plerixafor are mild and transient, which can overcome the adverse events due to G-CSF. This review assessed the current role and effects of plerixafor in stem cell mobilization for autologous and allogeneic stem cell transplantations.

Keywords: stem cell mobilization, apheresis, autologous stem cell transplantation, allogeneic stem cell transplantation

Introduction

Stem cell transplantation (SCT) is an established treatment for many hematologic malignancies. The proportion of patients requiring SCT is still increasing. In 2010 >30,000 patients received SCT in Europe. Meanwhile in 2019 >48,000 SCTs were performed; 59% were autologous and 41% allogeneic SCT. Autologous SCT was commonly performed for plasma cell disorders (55%) and lymphoma (36%) and the main indications for allogeneic SCT were acute leukemia (54%) followed by myelodysplastic syndrome (MDS) (12%).¹

Hematopoietic stem cells are collected from the bone marrow or the peripheral blood. Hematologic recovery is faster and morbidity is lower if stem cells are collected from the peripheral blood. In addition, promoting patient's comfort the use of peripheral blood is preferred for a SCT. CD34, a surface marker, is expressed on progenitor stem cells. The number of CD34+ cells in the peripheral blood is used for monitoring

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the collection time of the peripheral blood stem cells and is a reliable predictor for a successful stem cell mobilization. Peripheral CD34⁺ cell count is correlated with the number of collected CD34⁺ cells.^{2,3} CD34⁺ cells can be yielded from peripheral blood after mobilization via apheresis. The most commonly used agent for stem cell mobilization is granulocyte colony-stimulating factor (G-CSF); it is injected subcutaneously for several days until sufficient CD34⁺ cells are measured in the peripheral blood.

Under normal conditions the number of CD34⁺ cells in the peripheral blood is negligible (only <0.05% of the total leukocyte count). After mobilization with G-CSF this increases up to 5–15 times and the CD34⁺ cells accounted for up to 6% of the total leukocyte count.⁴ If the pre-apheresis CD34⁺ count is <5×10⁹/L, sufficient stem cell collection is not likely. If the CD34⁺ count is >20×10⁹/L the chance of collecting sufficient stem cells in one apheresis session is >90%.⁵ A position statement by the European Group for Blood and Marrow Transplantation mentioned that a pre-apheresis CD34⁺ count >20×10⁹/L is sufficient to start stem cell collection.⁶ Whereas in patients with a pre-apheresis CD34⁺ count between 10–20 × 10⁹/L the collection of sufficient stem cells can be frequently achieved with >1 apheresis sessions.^{6,7}

Stem cells can be mobilized either with (chemomobilization) or without chemotherapy. In mobilization without chemotherapy, G-CSF is administered for 4 days after

disease-specific chemotherapy and stem cells are collected by apheresis on day 5, if the CD34⁺ cells in the peripheral blood are > 20×10⁹/L (Figure 1A). In chemomobilization, G-CSF is administered after the mobilization-chemotherapy until there are sufficient CD34⁺ cells for a successful stem cell collection (Figure 1B). Therefore, with chemomobilization the timing of stem cell collection is unpredictable. In addition, there is a higher risk of bone marrow damage and toxicity resulting in more hospitalization. Nonetheless, chemomobilization results in a higher mobilization yield and has an anticancer effect.⁸ In patients with non-Hodgkin's lymphoma (NHL) disease-specific chemotherapy followed by stem cell mobilization is the preferred strategy, which is effective and avoids additional chemomobilization in these heavily treated patients.⁶ In patients with multiple myeloma (MM) chemomobilization with high-dose (≥3 g/m²) cyclophosphamide is the most commonly used strategy. However, a recent study reported that chemomobilization with low-dose cyclophosphamide (2 g/m²) is a safe mobilization regimen with stem cell collection rates comparable to that of high-dose cyclophosphamide.⁹ Further, healthy donors are mobilized with G-CSF 1–2 daily subcutaneous injections for 4–5 days (Figure 1C).

A collection of CD34⁺ cell count of ≥2×10⁶/kg is considered as sufficient for a SCT. Nevertheless, transplantations with a CD34⁺ cell count of ≥5×10⁶/kg are

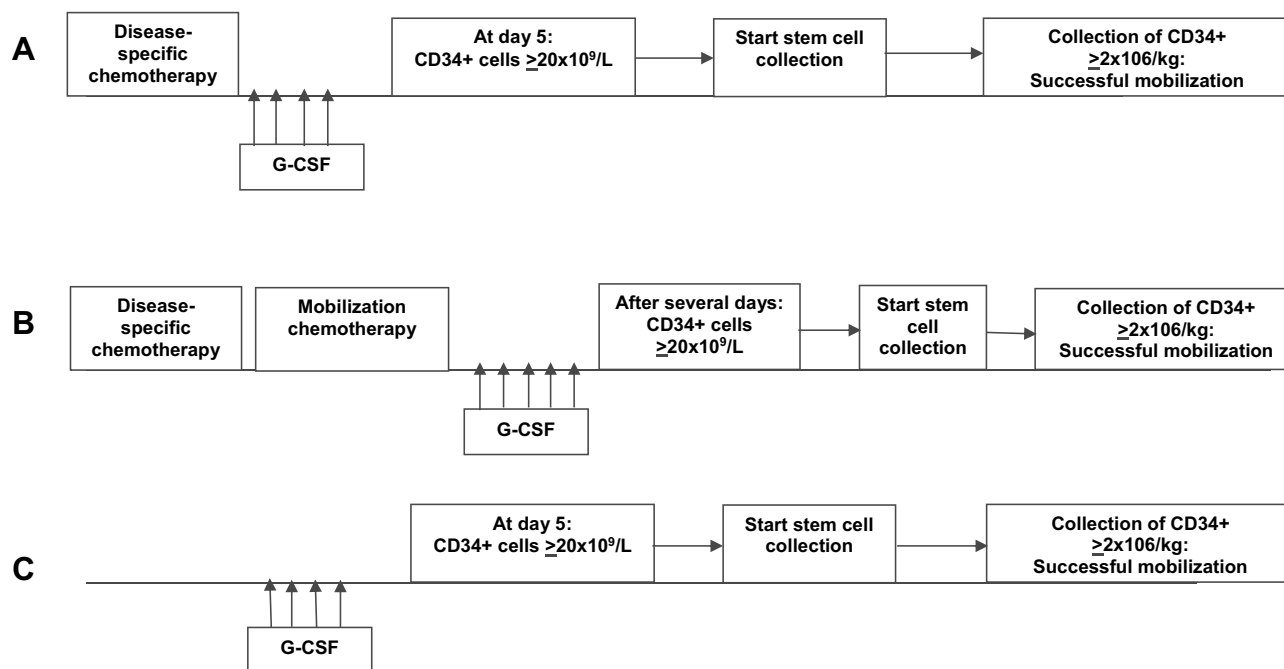


Figure 1 Strategies for stem cell mobilization in practice. Possible strategies in stem cell mobilization: with G-CSF only (A), with chemotherapy (B), in healthy donors (C). **Abbreviation:** G-CSF, granulocyte colony-stimulating factor.

associated with faster hematopoietic recovery, thereby resulting in a lower incidence of blood transfusions and shorter hospital stay.¹⁰ Further, a recent study showed a better 5-year overall survival when the patients are transplanted with higher number of CD34+ cells ($>2.65 \times 10^6/\text{kg}$).¹¹

Mobilization Failure Among Patients and Donors

Mobilization failure is defined as not able to collect $2 \times 10^6/\text{kg}$ CD34+ cells.¹² Mobilization failure is an important issue and has significant consequences among patients. The incidence of mobilization failure among patients is not fully documented, however the rate varies between 6% and 23%.^{8,13} These patients cannot receive an autologous SCT and, subsequently, cannot be treated adequately. This has a significant impact on outcome with a 3-year survival rate of 33% in patients with mobilization failure and 71% in those with a successful mobilization.¹⁴ A second attempt to remobilize with G-CSF is not effective and has a high failure rate. In a previous study only 23% of patients collected sufficient CD34+ cells with remobilization with G-CSF.¹⁵ Mobilization failure is associated with several factors including age, advanced disease, premobilization platelet count $<100 \times 10^9/\text{L}$, multiple chemotherapy lines, previous radiotherapy, pretreatment with alkylating agents, purine analogs or immune-modulators, diabetes and smoking.^{4,7}

The Italian Group for Stem Cell Transplantation GITMO (Gruppo Italiano Trapianto di Midollo Osseo) developed definitions for patients with mobilization failure.¹⁶ Patients with peripheral blood CD34+ cells $<20 \times 10^9/\text{L}$ after adequate mobilization with G-CSF and patients who are not able to collect $2 \times 10^6/\text{kg}$ after ≤ 3 apheresis are characterized as proven poor mobilizers. Further, patients are defined as predicted poor mobilizers if they had a previous mobilization failure, they previously received extensive radiotherapy or they met two of the following criteria: advanced disease (≥ 2 lines of chemotherapy), refractory disease, extensive bone marrow involvement or cellularity $<30\%$ at time of mobilization or age ≥ 65 years.

In contrast, in healthy donors mobilization failure with G-CSF is uncommon, with an estimated incidence rate between 5% and 10%.¹⁷ Female gender, older age, low weight and premobilization low leukocyte count were associated with mobilization failure among donors.¹⁸

Most donors experienced side effects after administration of G-CSF ($>80\%$); which commonly include bone pain, headache, fatigue and nausea/vomiting.¹⁹ Further, transient splenomegaly and even spleen rupture are observed.²⁰

Use of Plerixafor for Autologous SCT

Plerixafor (AMD3100) is a bicyclam molecule, which reversibly blocks chemokine receptor-4 (CXCR-4), thereby inhibiting binding with its ligand stromal-cell-derived factor-1 (SDF-1). This mechanism results in the release of hematopoietic progenitor cells in the blood circulation.²¹ Randomized (phase III) trials including patients with MM and NHL have shown that addition of plerixafor to upfront mobilization was associated with significantly higher CD34+ cells.^{22,23} Patients with MM have a higher CD34+ cell count than those with NHL (71% vs 59%). The two trials were followed by compassionate use programs in patients with mobilization failure with G-CSF. These patients received G-CSF in combination with plerixafor in a remobilization attempt; the success rates varied from 60% to 80%.²⁴ Based on these studies the use of plerixafor in patients with mobilization failure with G-CSF was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Several approaches with the use of plerixafor were investigated in patients with (predicted) mobilization failure: pre-emptive and risk-adapted approaches and in a second attempt to mobilize. The possible approaches are depicted in Figure 1. Plerixafor is added in the pre-emptive approach for patients with predicted mobilization failure based on pre-apheresis CD34+ cell count. Plerixafor is recommended in the mobilization scheme when the targeted CD34+ cell count in the peripheral blood is $<10 \times 10^9/\text{L}$ on days 4–5 of mobilization with G-CSF alone. If the CD34+ cell count is $<10 \times 10^9/\text{L}$ in patients with chemomobilization after 12–14 days, the incidence rate of predicted mobilization failure is high.²⁵ Therefore, in these patients plerixafor is recommended if the CD34+ cell count in the peripheral blood is $<10 \times 10^9/\text{L}$ and the leukocyte count is increasing. In patients with CD34+ cell count between $10\text{--}20 \times 10^9/\text{L}$ a dynamic approach is suggested based on patient's characteristics and treatment history.^{6,7} In these patients apheresis can be started and plerixafor is mandatory if insufficient CD34+ is collected ($<2 \times 10^6/\text{kg}$). In addition, plerixafor is recommended when $<25\%$ of the targeted CD34+ cells is collected on the first day of apheresis (Figure 2A).^{6,7}

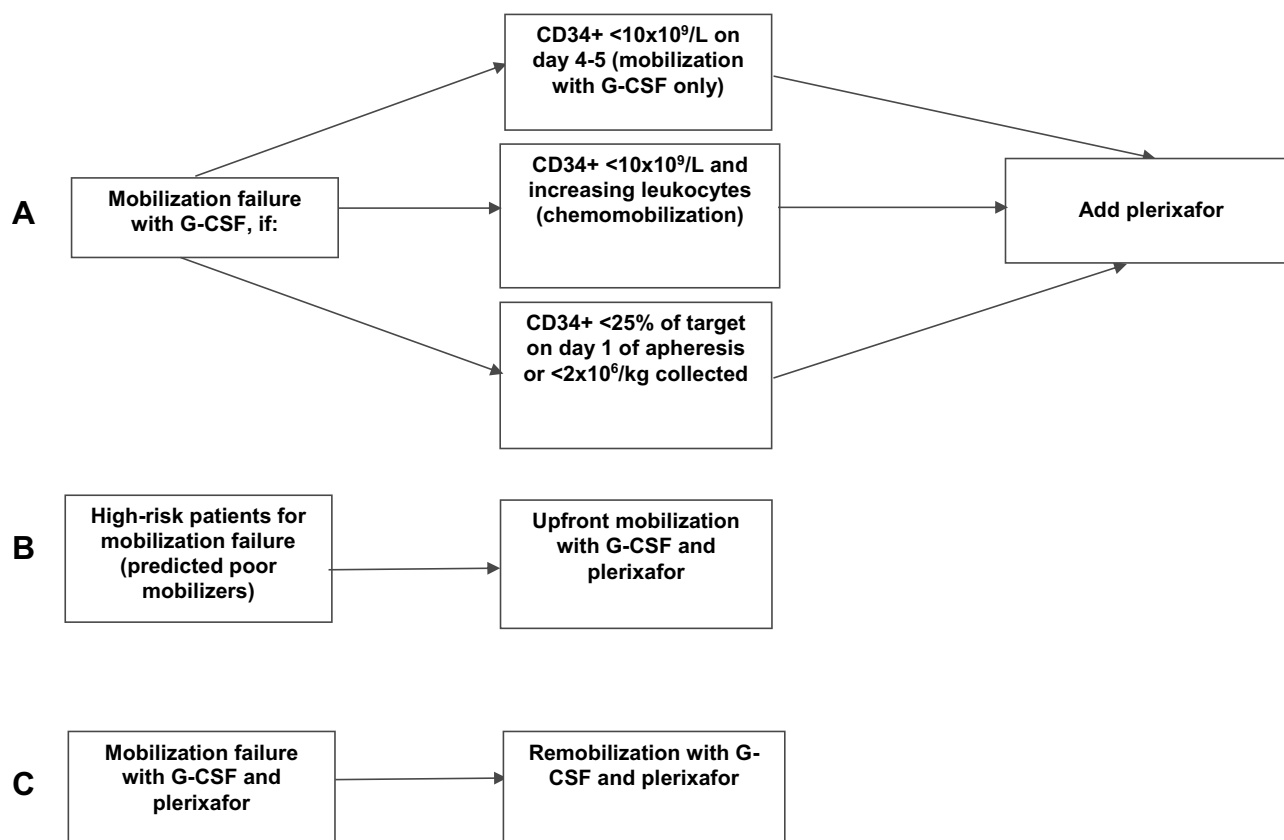


Figure 2 Approaches for use of plerixafor in patients with (predicted) mobilization failure. Approaches for the use of plerixafor: after mobilization failure with G-CSF (**A**), in patients with high-risk for mobilization failure with G-CSF (**B**), in patients with mobilization failure with G-CSF and plerixafor (**C**).

Abbreviation: G-CSF, granulocyte colony-stimulating factor.

Several studies showed that this pre-emptive approach resulted in almost 4-fold increase in CD34+ cells in the peripheral blood after administration of plerixafor, with mobilization rates of >90%.^{26–28} In another approach plerixafor is administered to patients who are at high-risk for mobilization failure (predicted poor mobilizers) based on baseline characteristics (Figure 2B). A low failure rate (~4%) was observed with this approach as well.²⁸ Until now, it is not clear which approach is superior. Both approaches were compared in two nation-wide surveys (in France and Canada). In both studies the success rates of both approaches were comparable (>70%).^{29,30} However, more studies should be performed to investigate the optimal use of plerixafor in patients with (predicted) mobilization failure.

Some studies investigated the effect of plerixafor in a second remobilization attempt after previous failure with plerixafor (Figure 2C). Also, in these studies high success rates (66–83%) were achieved.^{31,32} In one analysis pretreatment with fludarabine, low premobilization platelet count (<140×10⁹/L), age >65 years and radiotherapy were

significant predictors of mobilization failure with plerixafor.³³ Other studies revealed that patients receiving fludarabine- and lenalidomide-based induction regimens required higher number of plerixafor administrations to achieve a successful mobilization.^{34,35} To date novel drugs are used in induction therapy among patients with hematologic malignancies. Daratumumab, a novel monoclonal CD38 antibody, is increasingly administered to transplant-eligible newly diagnosed myeloma patients. In one study patients who received daratumumab during induction therapy required significant more administrations of plerixafor for a successful mobilization than in those who did not received it (21.7% versus 7.9%).³⁶ Further, the effects of the novel drugs in hematologic diseases should be elucidated in the future.

Patients with a very low pre-apheresis CD34+ cell count (<5×10⁹/L) have a significantly low probability for a successful mobilization. Even in these patients the addition of plerixafor was beneficial. The success rate was >70% in patients with a pre-apheresis CD34+ count of <5×10⁹/L.³⁷ In another analysis, mobilization was

successful in about 50% of patients with pre-plerixafor CD34+ cell count of $0-1 \times 10^9/L$ and $>70\%$ of those with a CD34+ cell count $>2 \times 10^9/L$.³⁴ Plerixafor is recommended to be injected subcutaneously 9–11 hours before the planned apheresis. Some studies have shown that the peak of CD34+ cells with plerixafor was observed at an earlier time (3 and 8 hours) in patients with poor mobilization.^{38,39} Therefore, in these patients the peak of CD34+ cells can be missed and consequently sufficient CD34+ cells cannot be collected. One recent study has shown that the efficacy is higher if apheresis was performed on the same day as the administration of plerixafor.⁴⁰ However, there are limited studies regarding the effect of plerixafor on the kinetics of stem cell mobilization.

To date plerixafor is widely used in patients with MM and NHL with mobilization failure with G-CSF. Further, plerixafor improved mobilization rates in patients with other diagnoses. In patients with Hodgkin's lymphoma the success rate was 74%.⁴¹ This was even higher in patients with nonhematologic malignancies (85%) and in children with malignant diseases (87%).^{42,43} In addition, plerixafor was successful for the purpose of gene therapy in sickle cell disease.⁴⁴ Due to the possible mobilization of leukemic cells plerixafor is not recommended for acute myeloid leukemia (AML). Although a recent small study showed a successful mobilization with plerixafor in 5 (minimal residual disease negative) AML patients with mobilization failure.⁴⁵

With plerixafor-induced mobilization more immature CD34+/CD38-cells and T- and NK-cells are collected, which can lead to faster hematopoietic recovery after transplantation.^{46,47} Few studies have shown that the grafts of MM patients had a higher number of NK-cells and CD19+ cells than those of NHL patients. However, no difference was observed in recovery.^{48–50} Further, the long-term effects of mobilization with plerixafor compared with G-CSF did not differ in progression-free survival or 5-year survival.⁵¹ However, one study showed that 5 of 43 patients developed secondary MDS or AML 29 months after an autologous SCT.⁵²

The administration of plerixafor is well tolerated and $<2\%$ of patients reported adverse events. Of which the most common were nausea/vomiting, diarrhea, fatigue, and headache. All adverse events resolved immediately and there were no grade 3 or 4 events.⁵³ Plerixafor is costly, this might be an important factor in the use among patients with mobilization failure. However, some

studies have shown that patients who received plerixafor required less apheresis sessions, which can equalize the costs of plerixafor.^{54,55} Moreover, lower cost was mentioned in cost-simulation analyses in patients with upfront stem cell mobilization with plerixafor compared to G-CSF.^{56,57} More studies are warranted to evaluate the cost-effectiveness of plerixafor.

Plerixafor for Allogeneic SCT

The use of plerixafor is not approved for allogeneic SCT. Since 2011 several case reports mentioned for the first that donors had a successful mobilization using plerixafor after mobilization failure with G-CSF.^{58,59} In the last years few studies have investigated the role of plerixafor among healthy donors.

In human leukocyte antigen (HLA)-identical and haplo-identical donors plerixafor was administered using several approaches: upfront,^{60,64,66,67} pre-emptive after failure with G-CSF,^{61,62,65,68,69} or remobilization after mobilization failure with G-CSF.⁶³ Moreover plerixafor was used successfully for haplo-identical SCT requiring a higher number of CD34+ cells.^{61,62,65} The characteristics of these studies are depicted in Table 1. In studies with upfront approach the median collected CD34+ after single injection with plerixafor was $2.9 \times 10^6/kg$ to $4.7 \times 10^6/kg$. Although the failure rate with a single injection with plerixafor was high (33% to 48%) and subsequently a second gift of plerixafor was necessary to achieve a successful stem cell collection. In two studies published in 2021 plerixafor was added pre-emptively to the mobilization with G-CSF.^{68,69} The peripheral CD34+ cell count showed 2.9-fold and 3.4-fold increases after adding a single injection of plerixafor. In these two studies, the collected CD34+ cells was $1.1 \times 10^6/kg$ and $1.6 \times 10^6/kg$ with G-CSF alone and it was raised to $2.8 \times 10^6/kg$ and $4.9 \times 10^6/kg$ with the combination G-CSF and plerixafor. Therefore, these studies suggest that if the collected CD34+ cells are not sufficient for an allogeneic SCT, addition of a single injection of plerixafor to the mobilization with G-CSF can be effective. Further, in some studies with healthy donors plerixafor was administered at different doses (0.24 mg/kg or 0.32 mg/kg). In one study plerixafor was administered at a higher dose (0.48 mg/kg) resulting in a higher peak of CD34+ cells, indicating that this might improve harvesting.⁷⁰ In contrast, another study showed no difference in failure rates in patients who were injected intravenously with higher doses of plerixafor (0.32 mg/kg) compared with those who were subcutaneously injected

Table I Studies with Plerixafor for Allogeneic Stem Cell Transplantation

Author/ Year	No. Donors	Transplantation Setting	Mobilization Setting	Plerixafor Dose	CD34+ in PB After 1 Gift Plerixafor (Median; x10 ⁹ /L)	Failure After 1 Gift Plerixafor	Total CD34+ Collected (Median; x10 ⁶ /kg)
Devine/ 2008 ⁶⁰	25	HLA-identical siblings	Upfront	0.24 mg/kg sc	16	33%	2.9
Hauge/ 2014 ⁶¹	6	Haplo-identical (n=4)/ HLA-identical (n=2) donors	Pre-emptive	0.24 mg/kg sc	Too small sample size	None	Too small sample size
Gattilo/ 2015 ⁶²	10	Haplo-identical (n=8)/ HLA-identical (n=2) donors	Pre-emptive (n=8)/ contraindication to G-CSF (n=2)	0.35 mg/kg sc	41	Not documented	2.8
Fiala/ 2016 ⁶³	32	Not documented	Remobilization	Not documented	30	None	7.1
Schroeder/ 2017 ⁶⁴	21	HLA-identical siblings	Upfront, Phase 1	0.24 mg/kg sc	Not documented	33%	3.5
Schroeder/ 2017 ⁶⁴	29	HLA-identical siblings	Upfront, Phase 2	0.32 mg/kg iv	Not documented	34%	2.9
Jaiswal/ 2017 ⁶⁵	26	Haplo-identical donors	Pre-emptive	0.24 mg/kg sc	136	0%	2.7
de Greef/ 2019 ⁶⁶	23	HLA-identical siblings	Upfront	0.32 mg/kg sc	26	48%	3.3
Chen/ 2019 ⁶⁷	64	HLA-identical siblings	Upfront	0.24 mg/kg sc	19	30%	4.7
Holig/ 2021 ⁶⁸	37	HLA-identical donors	Pre-emptive	0.24 mg/kg sc	44	43%	3.7
Cid/ 2021 ⁶⁹	30	HLA-identical donors	Pre-emptive	0.24 mg/kg sc	55	17%	4.2

Abbreviations: HLA, human leukocyte antigen; G-CSF, granulocyte colony-stimulating factor; sc, subcutaneous; iv, intravenous; PB, peripheral blood.

with plerixafor (0.24 mg/kg).⁶⁴ More studies should be conducted to investigate the use of plerixafor for an allogeneic SCT.

In addition, among donors the use of plerixafor is well tolerated. About 60–70% presented grade 1–2 adverse events and no donor experienced grade 4 events. The most common events were tingling, pain, fatigue, nausea, diarrhea, abdominal bloating and injection site reactions.^{66,68} All events resolved immediately, in contrast with G-CSF no bone pain was observed after administration of plerixafor.⁶⁷ This suggests that the adverse events of administration of G-CSF for multiple days can overcome with one or two injections of plerixafor. Further, it has been suggested that viral infections can negatively influence stem cell mobilization with G-CSF. In one case-report sufficient CD34+ cells was collected with single gift of plerixafor in a donor with influenza A and mobilization failure with G-CSF.⁷¹ Nevertheless, the possible effects of the

COVID-19 pandemic on mobilization failure should be evaluated in the future.

Immunologic studies have shown higher CD3+ and CD4+ cell counts in grafts mobilized with plerixafor, however there was no increase in the incidence of graft-versus-host disease.⁷² Some studies have shown that in allogeneic SCT engraftment of neutrophils and platelets after stem cell mobilization with plerixafor was faster than that with mobilization failure with G-CSF.^{67,73}

Future Directions

Plerixafor was the first drug that has been approved for patients with mobilization failure. In recent years, early phase or preclinical trials were conducted to assess the efficacy of novel agents. The use of POL6326, a CXCR-4 antagonist, was effective based on a Phase II trial conducted on myeloma patients,⁷⁴ and another CXCR-4

antagonist, BKT140, was found to be associated with a 78-fold increase in the number of stem cells.⁷⁵ Moreover, it was even more effective than the combination of G-CSF and plerixafor. Parathormone (PTH), SEW2871, a sphingosine-1 phosphate agonist, and BIO5192, an inhibitor of VLA-4/VCAM, increased the number of stem cells in mobilization in animal studies.⁷⁶ However, the use of more novel agents with promising results among healthy donors and animals are still investigated.

Conclusions

SCT is a well-established for patients with hematologic malignancies. Mobilization failure is an important issue as it is associated with poor survival. Plerixafor is the first agent approved for patients with mobilization failure with G-CSF. The success rates are high. Therefore, more patients can be treated adequately with autologous SCT. In patients with pre-apheresis very low CD34+ cell count plerixafor is effective. Plerixafor is well tolerated with mild adverse events which resolve immediately. However, there is no consensus on the optimal approach with plerixafor in patients with mobilization failure with G-CSF. The use of plerixafor for allogeneic SCT plerixafor has not been approved yet. Only few studies have shown that plerixafor is efficient among donors. Moreover, the adverse events of G-CSF can be overcome with the use of one or two injections of plerixafor among donors. To assess the optimal use of plerixafor for autologous and allogeneic SCTs more clinical, immunologic and cost-effectiveness studies should be conducted. Further, the effects of the COVID-19 pandemic in stem cell mobilization must be elucidated in the future.

Disclosure

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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