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REVIEW

Hematopoietic stem cell mobilization strategies to support high-dose chemotherapy: A focus on relapsed/refractory germ cell tumors

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Abstract

High-dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplantation has been explored and has played an important role in the management of patients with high-risk germ cell tumors (GCTs) who failed to be cured by conventional chemotherapy. Hematopoietic stem cells (HSCs) collected from the peripheral blood, after appropriate pharmacologic mobilization, have largely replaced bone marrow as the principal source of HSCs in transplants. As it is currently common practice to perform tandem or multiple sequential cycles of HDCT, it is anticipated that collection of large numbers of HSCs from the peripheral blood is a prerequisite for the success of the procedure. Moreover, the CD34+ cell dose/kg of body weight infused after HDCT has proven to be a major determinant of hematopoietic engraftment, with patients who receive > 2×10^6 CD34+ cells/kg having consistent, rapid, and sustained hematopoietic recovery. However, many patients with relapsed/refractory GCTs have been exposed to multiple cycles of myelosuppressive chemotherapy, which compromises the efficacy of HSC mobilization with granulocyte colony-stimulating factor with or without chemotherapy. Therefore, alternative strategies that use novel agents in combination with traditional mobilizing regimens are required. Herein, after an overview of the mechanisms of HSCs mobilization, we review the existing literature regarding studies reporting various HSC mobilization approaches in patients with relapsed/refractory GCTs, and finally report newer experimental mobilization strategies employing novel agents that have been applied in other hematologic or solid malignancies.

Key Words: Hematopoietic stem cells; Germ cell tumors; Hematopoietic stem cell transplantation; Granulocyte colony-stimulating factor; Plerixafor

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Core tip: High-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) is a curative treatment option for patients with relapsed/refractory germ cell tumors (GCTs). Mobilization of adequate numbers of hematopoietic stem cells (HSCs) is a prerequisite for successful ASCT. As the benefit of HDCT+ASCT is largely evident with > one HDCT cycle, it is anticipated that an appreciable percentage of patients will not mobilize adequate HSCs and require salvage strategies. Herein, we review the history of HSC transplantation, with emphasis in GCTs, pathophysiological mechanisms of HSC mobilization, initial and salvage mobilization strategies, and finally discuss novel mobilizing agents and approaches to overcome failures.

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INTRODUCTION

High-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (ASCT) has been a major breakthrough in oncology. It has broad applicability in patients with metastatic germ cell tumors (GCTs) who experience one or even more relapses after previous chemotherapy, or in those with a poor prognosis on diagnosis (*e.g.*, with extragonadal primary or incomplete response to first-line cisplatin-based chemotherapy)[1,2]. The efficacy of HDCT and ASCT depends largely on successful and adequate hematopoietic stem cell (HSC) mobilization, which ensures faster neutrophil and platelet engraftment and therefore decreased infection risk and hospitalization[2]. Collection of at least 2.0 × 10^6 CD34+ HSCs has been considered the minimum for a subsequent successful ASCT[3,4]. However, successful mobilization remains a great challenge, as a significant number of patients, somewhere between 5%-30%, are unable to mobilize enough HSCs to support subsequent ASCT. That has been attributed to extensive and prolonged prior exposure to bone marrow-suppressing intensive chemotherapy that has ultimately led to poor bone marrow reserves [5]. Indications, as far as strategies appropriate for achieving adequate CD34+ cell numbers for these patients, are limited by a lack of data and are generally based on standard approaches for HSC mobilization that have been applied in other disease settings. Hence, the establishment of standard mobilization and remobilization techniques for patients with GCTs who failed the initial mobilization protocols should become a high priority (outlined in Figure 1).

GERM CELL TUMORS

Testicular cancer and GCTs typically subdivided into two main histologic subtypes, seminomas and non-seminomas, are the most common solid tumor in men between 20 and 35 years of age[6,7]. Approximately 50% of testicular cancers are non-seminomas, which are typically more malignant and usually associated with a more aggressive clinical presentation[8]. The cure rates are between 41%-92%[9,10]. About 20%-30% of patients with metastatic disease at initial presentation will eventually require salvage treatment. Second-line therapy options include conventional dose cisplatin-based regimens, or high-dose chemotherapy regimens, currently consisting of carboplatin and etoposide plus ASCT support[10,11].

To date, the main conventional dose chemotherapy (CDCT) salvage regimens include etoposide-ifosfamide-cisplatin, vinblastine-ifosfamide-cisplatin, and paclitaxel (taxol)-ifosfamide-cisplatin (TIP)[12,13]. Randomized data are lacking, and retrospective comparisons have failed to demonstrate the superiority of any of these regimens. Nevertheless, the best results were observed with TIP, which is therefore currently broadly accepted as the optimal choice of salvage chemotherapy.

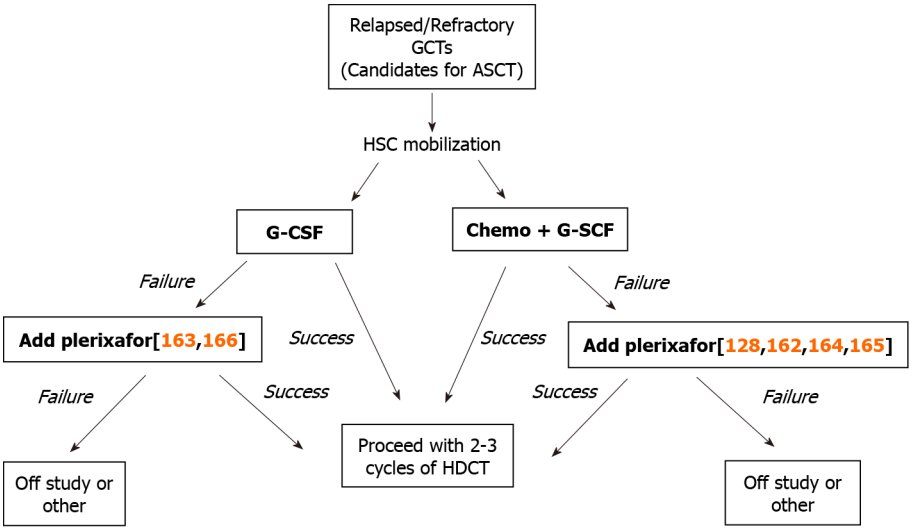

Figure 1 Mobilization algorithms. ASCT: Autologous stem cell transplantation; G-CSF: Granulocyte colony-stimulating factor; GCTs: Germ cell tumors; HDCT: High-dose chemotherapy; HSC: Hematopoietic stem cell.

CURRENT STATUS OF HDCT AND ASCT IN GERM CELL TUMORS

In HDCT, cytotoxic agents are administered at much higher doses than the standard dose applied in CDCT. The observation of a larger therapeutic impact even at minor increases of dosage, proved the dose-response relationship of many chemotherapeutic agents, and thus supported the efficiency of HDCT regimens in eradicating residual drug-resistant tumor cells[14]. Increased doses lead also to more severe side effects, with prolonged myelosuppression being the main reason to delay subsequent cycles, thus leading to failure[15]. To reduce the duration of pancytopenia, and therefore the failure rate, HSCs are harvested from the patient's peripheral blood by apheresis before the administration of HDCT. After completion of HDCT the harvested stem cells are reinfused to repopulate the bone marrow and ultimately re-establish hematopoiesis. Despite the fact that the use of HDCT as salvage in GCTs is a standard treatment option for most patients, its efficacy as a first salvage strategy remains a matter of debate among investigators[16-19]. An ongoing phase III trial - the TIGER study - may be the first to establish HDCT as initial salvage in these patients, considering the existing inconsistent evidence as well as the lack of conclusive randomized trials.

HISTORY OF ASCT

Total-body irradiation (TBI) prior to autologous transplantation was first applied in animals in the 1930's. The early studies had fatal outcomes because of severe gastrointestinal and nervous system complications, hemorrhage, and infection[1,2]. Similar trials of TBI were performed in humans few years later. The first was performed by Thomas and his colleagues in a leukemic patient, who was grafted with bone marrow from her identical twin sister. They reported a 3-month remission duration in this patient. Following the discovery of the human leucocyte antigen (HLA) system by Dausset in 1958[20], the concept of histocompatibility, *i.e.* identical HLA in both the donor and recipient (patient),was applied, with high success rates for allogeneic transplantations.

STEM CELL SOURCES-DIFFERENCES BETWEEN PERIPHERAL BLOOD HSCs AND BONE MARROW HARVESTING

Bone marrow was the first source of HSCs, which were obtained by repeated aspirations from the posterior iliac crests with the donor under general or local anesthesia. The method was used for many years until the observation that stem cells detach, enter the circulation and home to the marrow. After that observation, peripheral blood

harvesting, as more convenient and appropriate source of HSC, has replaced bone marrow[1]. There are two types of peripheral blood leukapheresis, normal volume and large volume. The normal volume procedure processes 2.5 to 3 times the patient blood volume. The large volume procedure processes 4-5 times the volume. Many researchers evaluated the efficacy and safety of large volume leukapheresis and concluded that, after successful mobilization, this leads to a higher CD34+ cell harvest without a change in graft quality ,with fewer sessions to reach greater than 2 × 10^6 CD34+ cells/kg body weight[3,4,21].

Goldman *et al*[22] was the first to use HSCs collected from the peripheral blood for autologous transplantation after high-dose cytotoxic therapy in patients with CML. Körbling *et al*[23] followed with a report of autologous transplantation in a patient with CML, and a patient with Burkitt's lymphoma. Körbling *et al*[23] reported the collection of peripheral blood stem cells after the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) during leukocyte recovery after myelosuppressive chemotherapy. That was the first example of chemotherapy-induced "mobilization". Subsequently Kessinger *et al*[24] used the same mobilization method and documented that performing multiple leukapheresis sessions resulted in a sufficient number of circulating HSCs in the peripheral blood to ensure engraftment after HDCT.

DIFFERENCES BETWEEN PERIPHERAL BLOOD HSC AND BONE MARROW HARVESTING

Traditionally, as HSCs reside in the bone marrow at steady-state conditions, collection has been carried out by bone marrow harvesting from the posterior iliac crests and possibly the sternum under general or epidural anesthesia[25]. Bone marrow harvesting, as mentioned earlier, is a one-time procedure with multiple risks that increase with donors age and comorbidities. Peripheral blood HSC (PBSC) collection performed by large-volume leukapheresis, is dependent on stem cell mobilization, and a prolonged harvesting period is required. However it is considered safe to perform on donors without the need of any type of anesthesia. A limitation of PBSC collection is adequate venous access. PBSC collection performed by single or multiple apheresis avoids the risks of general anesthesia and shortens the time for hematopoietic recovery. The most common adverse effects include moderate-to-severe bone pain as a result of leucocyte growth factor administration, fatigue, and headache. Rare adverse events include splenic rupture, acute arthritis, anaphylaxis, and cardiac ischemia[26-28].

Since the early 90's, HSCs mobilized from the bone marrow into the peripheral blood (PB) have been established as the preferred source of HSCs for transplantation because they are easily accessible, and the evidence indicates that they engraft faster after transplantation than HSCs directly harvested from bone marrow (BM). Clinical findings from randomized/comparative trials indicate that patients experience faster neutrophil, platelet, and immune recovery after PB stem cell transplantation; and in allogeneic transplantation, a higher incidence of chronic graft *vs* host disease and lower probability of relapse[29].

HSCS MOBILIZING AGENTS

HSCs are multipotent precursors with self-renewal potency that reside predominantly in the bone marrow. A small number of HSCs circulate in the blood (< 0.02%) under steady-state conditions[30]. Several methods have demonstrated effectiveness in increasing the percentage of HSCs in PB and maximize the number collected with the intention of restoring marrow function and reduce the time required for neutrophil and platelet engraftment following HDCT. Initial mobilization strategies include: (1) Administration of hematopoietic CSFs alone; (2) A course of myelosuppressive chemotherapy prior to collection; and (3) Chemotherapy followed by cytokine administration. Remobilization strategies include: (1) Dose escalation of leucocyte CSFs; granulocyte (G)-CSF or granulocyte-macrophage (GM)-CSF, with or without IL-3; (2) Different forms of G-CSF, with altered glycosylation patterns to improve pharmacokinetics and bioavailability; (3) G-CSF in combination with other HSC mobilizing agents, *i.e.* Plerixafor or stem cell factor (SCF), *kit*-ligand (known as ancestim); and (4) G-CSF in combination with chemotherapy and newer agents like plerixafor. A course of myelosuppressive chemotherapy prior to HDCT as a chemo-mobilization strategy

not only increases stem cell collection, but also provides better control of the underlying malignancy, when active agents or chemotherapy regimens are administered [31,32]. However, an increased risk of infection and hospitalization is expected in patients undergoing chemo-mobilization[31].

In turn, the administration of mobilization agents alone not only has the benefit of relatively predictable kinetics of mobilization, but also a reduced need for hospital care compared with chemotherapy because of the minimal side effects of G-CSF[33,34]. The most commonly used myeloid growth factor for peripheral stem cell harvesting is G-CSF. Other alternatives are its pegylated form; pegfilgrastim, and sargramostim; the recombinant human GM-CSF. Several studies now confirm higher successful rates and twice as many progenitor cells in the circulation when a combination of chemotherapy and G-CSF is used. Consequently, that approach is favored by many investigators[35, 36].

Having said that, the use of newer agents, such as chemokine receptor antagonists, along with the conventional ways of autografting mentioned above has expanded in recent years, with promising synergistic results. Plerixafor, a bicyclam molecule derivative that reversibly competes with and inhibits stromal-derived factor-1a (SDF-1a; also known as CXCL12) binding to CXCR4, causes an absolute peak of CD34+ cells 6-9 h after administration. Administration is preferable in the evening before apheresis, ideally 8-10 h before the procedure to maximize the number of HSCs collected [37]. Daily administration of plerixafor in the evening for up to four consecutive days can be given, with a morning G-CSF dose along with the apheresis sessions if the desired HSC target number has not been achieved[38]. However, considering the higher cost of that approach, one recognizes the need to establish specific mobilization algorithms in order to maximize the potential of the conventional mobilization agents. That improves the pharmaco-economics of mobilization and reduces the need of rescue remobilization with plerixafor. Nowadays, because of its high cost, plerixafor use is restricted to patients failing to reach sufficient PB CD34+ cell counts (*i.e.* preemptive application) on the day that apheresis is planned to start or in patients failing to collect sufficient CD34+ cells during leukapheresis (*i.e.* rescue application). Preemptive use of plerixafor, especially in combination with G-CSF in poor mobilizers has proven to be more cost effective[39,40].

MOBILIZATION ALGORITHMS TO OPTIMIZE MOBILIZATION OUTCOMES

In patients with relapsed/refractory GCTs, we and others attempt HSC mobilization preferably after 1 or 2 salvage chemotherapy cycles with TIP or TI followed by the administration of G-CSF between days 3 and 11 or until the day when sufficient numbers of CD34+ HSCs have been obtained. This approach is accompanied by frequent measurement of circulating PB CD34+/μL counts by flow cytometry, usually starting on day 10-11, in order to decide when to perform the apheresis. A mobilization algorithm called the "just in time"[41] approach helps to decide whether the patient is in need of plerixafor. Patients with an absolute number of CD34+ cells > 3 and < 15/μL are the main candidates for plerixafor administration. Other protocols include "one size fits all"[42], in which a standard technique is applicable to all patients and "risk-based approaches"[43]. The latter places patients into categories, where those who meet more of the predefined criteria are more likely to be poor mobilizers, and thus a different approach must be used. Poor mobilizers are defined as those who have received many prior lines and cycles of chemotherapy, particularly those who have been exposed to alkylating agents, irradiation, pre-existing low blood counts, bone marrow involvement by the tumor, and advanced age[39,44].

UNDERSTANDING THE STEM CELL NICHE IS CRITICAL FOR FURTHER PHARMACOLOGICAL STUDIES

Schofield was the first to propose the concept of HSCs in 1978[45]. Since then, many have attempted to virtually define this area[46-49], and as a result, we now refer to stem cell niche as the microenvironment where localization and regulation of stem cells takes place. The area is anatomically located near to the endosteum and is composed by two major compartments, the perivascular and the endosteal niches, where cells and molecules dynamically interact[50,51]. The endosteal niche compartment consists of osteoblasts and is critical for supporting the lymphoid progenitors

[52]. It is a hypoxic environment that favors the undifferentiated state of HSCs[53], where low energy supplies are needed. Hypoxia is a critical component of the HSC niche[54], and exposure of HSCs to elevated oxygen tissues negatively affects self-renewal and promotes cell cycle entry, hindering low-cycling proliferation[54,55]. Low oxygen concentration in the endosteal niche is regulated by hypoxia-inducible factor-1 (HIF-1), a transcription factor, which under hypoxic conditions, binds in its full heterodimeric form (HIF1a + HIF1b) to DNA elements controlling transcription of various genes related to angiogenesis and erythropoiesis, resulting in the upregulation of vascular-endothelial growth (VEGF), which ultimately leads to vasodilation and HSC mobilization[56].

The vascular niche is rich in oxygen, and it is thought that HSCs migrating towards the niche proliferate and regenerate. This compartment is subcategorized into arterial-perivascular, mesenchymal, and sinusoidal endothelial niches. Recent studies showed that the arterial-perivascular niche mostly consists of nestin-bright (nestin+)-smooth muscle perivascular cells[57,58] that express high levels of CXCL12/SDF1 under steady-state conditions and therefore appear to be strongly associated with both proliferation and maintenance of primitive hematopoietic cells in a quiescent state[58,59]. The endothelial sinusoidal niche is composed of endothelial cells that are nestin-dim/leptin receptor-2 (LEPR2) and CXCL12-abudant reticular (CAR) cells with high amounts of CXC-L12, which contribute to regeneration after myelotoxic stress[58]. Several studies showed that as HSCs enter the cell cycle they relocate from areas rich in nestin-bright perivascular cells to those rich in LEPR2+ cells and are mobilized into the circulation[58-60]. In addition to cellular interactions, stem cells are attracted to the bone marrow niche cells through dynamic interactions involving soluble factors (*e.g.*, growth factors, chemokines and cytokines, and adhesion molecules).

One of the most critical chemotactic factors, SDF1a (CXCL12), mainly derived from osteoblasts and endothelial cells, attract HSCs by attaching to their surface chemokine receptor; CXCR4[61]. Other important adhesion molecules are VCAM1 (CD106), which binds to integrin α4β1, very late antigen-4 (VLA-4) on HSCs, and a transmembrane SCF that binds to c-kit (CD117) on HSCs[62,63]. It is well understood that the breaking down of those tethers is necessary for the release of HSCs into the circulation.

Other cells, such as adipocytes, and macrophages have supporting roles in the BM environment. CD169 macrophages secrete oncostatin-M, which leads to increased CXCL12 production by nestin+ and other mesenchymal cells *via* the MAPK-p38 signaling pathway[64,65]. Depletion of the macrophages results in downregulation of VCAM1, SDF1a, and SCF expression that disrupts the normal niche functions[64,65]. The percentage of adipocytes in the BM, derived from mesenchymal cells, increases with age, leading to a fatty marrow with limited cell proliferation ability[66].

INITIAL MOBILIZATION STRATEGIES

*Use of G-CSF or biosimilar**

Brief history: In 1966, Ray Bradley and Don Metcalf were the first to identify agents that can stimulate colony formation in hematopoietic cells in semi-solid culture[67]. Later, in 1985 Welte *et al*[68] purified human G-CSF. Nagata *et al*[69] in Japan and independently Souza *et al*[70] from AMGEN in 1986 cloned the G-CSF gene, resulting in the production and clinical application of this cytokine. The first preclinical data to demonstrate mobilization of hematopoietic cells following the administration of G-CSF in mice was in 1986 in a study conducted by Tamura *et al*[71], where an observation of increasing neutrophil counts approximately 2 h after injection made. The following year, Duhrsen *et al*[72], confirmed the mobilizing activity of G-CSF in cancer patients, where an increase of mature and progenitor cells into the circulation was observed. The observations were the stimuli for further animal studies to determine whether the progenitor cells could be effective for hematopoietic reconstitution[73].

Mechanism of action: The G-CSF receptor (G-CSFR) is expressed on a range of hematopoietic cells, including mature neutrophilic granulocytes, myeloid progenitors, and HSCs[74]. After binding to its ligand, receptor multimerization and activation of several intracellular signaling cascades occur, including the Jak/Stat/Socs, Ras/Raf/Erk and PI3-kinase/Akt pathways, which ultimately leads to transcriptional changes that have an impact on survival, migration, proliferation, and differentiation[74]. G-CSFR signaling also mediates the mobilization of hematopoietic progenitor cells (HPCs) and mature neutrophilic granulocytes from the bone marrow[75]. Multiple mechanisms have been described to explain the mechanism of action of G-CSF.

Because most of the topics are still poorly understood, further studies are required. It has been previously hypothesized that the mechanism of mobilization by G-CSF is indirect, based on the fact that HSCs themselves, in order to mobilize, do not express the G-CSFR receptor[76], which is mainly expressed on the surface of macrophages and osteomacs[77]. (1) The first mechanism includes the role of proteases. It is known that following G-CSF administration, an increase in the number of granulocytes occurs. The increase is accompanied by the production of large amounts of proteases such as neutrophil elastase, cathepsin, and MMP-9 by neutrophils[78], which in combination with other proteases, such as the CD26 dipeptidase[79], inactivate multiple adhesion molecules (VCAM1, CXCR4, fibronectin, c-kit, SCF, OPN), thereby disrupting their attachment to the VLA4 receptor and weakening intracellular adhesive interactions[80-83]. One of the most important mechanism is the induced proteolytic clearance and degradation of SDF1 (CXCL12) in the bone marrow. Matrix metalloproteinase (MMP)-9[84,85] and CD26 cause the cleavage of the NH2-terminal of SDF1, so it can no longer contact the surface CXCR4 receptor, leading to liberation of HSCs into the circulation[80,86]. In addition, type 1 metalloproteinase (MMP1) increases CD44 cleavage. CD44 ligand is hyaluronic acid, rich in endosteum and sinusoidal endothelium, and essential for HSCs homing[87]. (2) The second involves changes in bone formation. Following G-CSF administration, a variety of changes in bone formation occur, more specifically an almost complete loss of the osteoblastic layer has been observed[65,75,88]. Osteoblasts are essential in the BM microenvironment by producing cytokines, chemokines and adhesion molecules[89]. The osteoblasts, however, do not express the G-CSFR[88,90], which suggests that this effect is mediated by other cell types. Osteoclasts arise from HSCs and do express the G-CSF receptor, so it has been proposed that they play a critical role not only in formation of the hematopoietic niche, but also in HSC mobilization through secretion of cathepsin K, which cleaves and inactivates CXCL12[76,91]. However, the formation is no longer thought to be mainly the result of osteoclast activation, but rather to the loss of supporting cells, such as osteomacs and macrophages[65]. There is evidence that after administration of G-CSF, osteomacs leave the endosteal surface concurrent with endosteal osteoblast depletion[65]. (3) The third assumes a role of CD68/CD169 macrophages. The depletion of CD68/CD169+ macrophages seems to initiate a decreased expression of factors required for HSC retention (CXCL12), by selective downregulation of nestin+ mesenchymal stem cells (MSCs), as has been mentioned earlier[64,65]. That ultimately causes mobilization of HSCs into the PB. (4) The fourth involves complement activation. Activation of the complement cascade and thrombolytic pathway plays also a major role because of the release of sphingosine-1-phosphate (S1P) into the circulation by red blood cells, endothelial cells, and activated platelets. S1P is a strong chemoattractant of HSCs, creating an enabling environment for proliferation in the plasma[92,93]. S1P increases in blood and decreases in BM during mobilization, inhibiting SDF1 through the p38/Akt/mTOR pathway[92]. Both SDF1 and S1P are regulated by specificity protein (SP)-1, which it is thought to maintain a balance of their antagonistic effects. Several studies also suggest a role of the C5a complement component in mobilization, probably by neutrophil stimulation and the subsequent increase of MMP9 and decrease of CXCR4 expression. That is supported by the observation that C5-deficient mice respond poorly to G-CSF mobilization[94]. On the other hand, C3a expression promotes the chemotaxis of HSCs by CXCL12[94]. And (5) The fifth includes a role of the sympathetic nervous system. The role of the sympathetic nervous system (SNS) in G-CSF mobilization has been investigated. Sympathectomy or pharmacological innervation of the SNS[90] both lead to impaired mobilization in the mouse, and beta-2 (β2) agonist administration increases mobilization[90]. Another possible explanation is mobilization *via* nestin+ MSCs, which express many adhesion molecules, such as CXCL12, IL-17, and VCAM that are downregulated by β3 adrenoreceptor activation or G-CSF stimulation[95,96]. That observation explains why diabetes patients with impaired SNS function fail to mobilize adequate HSC numbers[97,98]. Summarizing, G-CSF upregulates CXCR4 in HPCs and decreases CXCL12 levels in the bone marrow relative to the blood and other tissues, establishing a chemo-attractive gradient that promotes migration of HSCs to the peripheral circulation.

Addition of chemotherapy as a mobilization strategy

For years there have been trials to establish a universal chemotherapeutic regimen, but without success because of uncontrolled or unknown variables. The optimal chemotherapeutic regimen for mobilization should have both antitumor activity and mobilization capacity[99]. Therefore, a chemotherapy regimen that is effective for the

underlying disease, either at relapse or first-line, in combination with G-CSF is used for PBSC mobilization. The main disadvantages are hematological toxicities, mobilization costs, and a rather unpredictable post-chemotherapy time for HSC harvest. Furthermore, it is essential to monitor the number of CD34 + cells in the PB every day. Considering the mechanism responsible for the effect of the chemotherapy regimens on bone marrow leading to stem cell mobilization, clear evidence exists only for cyclophosphamide (CY). Many studies have been conducted in humans, primates, and mice that showed release of active proteases in the bone marrow in response to G-CSF and CY[80,100]. The proteases cleave and inactivate many proteins that hold HSCs within the bone marrow stroma. CY increase the release of neutrophil proteases in the BM, with cleavage of VCAM-1 and decreased SDF-1a concentration in the BM. Winkler *et al*[101] demonstrated that CY induced a major reduction in SD-F1a mRNA ex-pression that promoted HSC mobilization without impairment of kit-ligand expression, indicating maintenance of niche functions and rapid recovery afterward. In addition, they observed a reduction in endosteal osteoblasts, bone formation, and F4/80+ osteomacs, while osteoid remained on the endosteum despite the absence of osteoblasts.

One of the often administered regimens is an intermediate dose of CY at 2-4.5 g/m^2, whereas high doses at 7 g/m^2 have been used as well, followed by the administration of G-CSF at a dose of 5-10 μg/kg/d[102]. Others used etoposide in combination with CY and/or cisplatin or added paclitaxel and concluded that the regimens were more effective for stem cell mobilization than CY alone. Moreover, Weaver *et al*[103] in 1998, used taxanes, either paclitaxel or docetaxel, in combination with CY, followed by G-CSF, and observed more efficient mobilization, almost three times more efficient than CY + G-CSF alone in patients with metastatic breast cancer[103].

The most frequently used regimen in patients with GCTs is paclitaxel at 200 mg/m^2 on day 1 plus ifosfamide at 2 g/m^2/d on days 1-3 (TI) supported with G-CSF at 10 μg/kg/d, starting on day 4[104,105]. TI was shown by Rick *et al*[104] more efficient than TI with the addition of cisplatin; *i.e.* the TIP regimen. An interesting mobilization regimen was used in the TAXIF study, wherein the epirubicin was added to paclitaxel. Despite the different chemotherapy mobilization regimens that have been used, the most commonly applied are TI or TIP, as was shown in a retrospective study by Hamid *et al*[106] (see also Table 1 for detailed references to the studies).

REMOBILIZATION STRATEGIES

Dose escalation of cytokines

Higher doses of G-CSF agents have been suggested as a strategy to improve mobilization and peripheral stem cell collection, but the evidence is conflicting. Some studies found no significant difference when a dose of 5 μg/kg/d was administered compared with the most broadly applied doses of 10 μg/kg[107,108]. Similarly, twice daily administrations did not demonstrate improved stem cell yields[109]. However a number of studies conducted in hematologic patients, provided compelling evidence that higher doses improved mobilization.

Structural modifications to improve poor physicochemical properties

Lenograstim: Lenograstim, a glycosylated form of G-CSF, also widely used for HSC transplantation, was hypothesized to induce increased mobilization compared to conventional G-CSF agents. In fact, it was proposed that its unique structure and glycosylation pattern provided protection against elastase-dependent inactivation, and could thereby lead to prolonged activity and increased mobilization[110,111]. Several studies though did not find any differences on HSC mobilization with collection results and patient outcomes comparable to conventional G-CSF-mobilized patients. Therefore, data on its efficacy remains to date both limited and inconclusive[112-114].

Pegfilgrastim: Pegfilgrastim is a pegylated form of G-CSF with long half-life characteristics because of its significantly reduced renal excretion[115]. It promotes stem cell mobilization with a single dose administration, as opposed to the daily injections of the regular short half-life G-CSF[116,117]. The results of recent studies have been controversial, as a number of them supported a significant increase in peripheral stem cells collected, while others found no difference in terms of stem cell mobilization, when a double dose of 12 mg-compared to the 6mg dose after conventional chemotherapy-was administered[118].

Table 1 Clinical studies applying various hematopoietic stem cell mobilization chemotherapy + granulocyte colony-stimulating factor protocols in patients with relapsed/refractory germ cell tumors

Ref.	Number of patients	Successful mobilization	Mobilization regimen
Fruehauf *et al*[149] 1995 (prospective analysis)	15	Median BM 31.49 × 10^6/kg PB 0.46 × 10^6/kg 100%	Cisplatin 100 mg/m^2 etoposide 75 mg/m^2 ifosfamide 2 g/m^2 + G-CSF
Tada *et al*[150] 1999 (retrospective analysis)	6	2.5 × 10^8/kg 100%	Cisplatin 200 mg/m^2 ifosfamide 4 g/m^2 etoposide 100 mg/m^2 d1-d3 + G-CSF
Rodenhuis *et al*[151] 1999 (multicenter prospective phase II)	35	10.3 × 10^6/kg 100%	Cisplatin 200 mg/m^2 ifosfamide 4 g/m^2 etoposide 100 mg/m^2 d1-d3 + G-CSF
Lotz *et al*[152] 2005 TAXIF 2005 (retrospective analysis)	45	9 × 10^6/kg (for 3 HDCT) 100%	Epirubicin 120 mg/m^2 - paclitaxel 200 mg/m^2 + G-CSF
Argawal *et al*[102] 2009 (retrospective analysis)	37	3-6 × 10^6/kg 100%	ifosfamide 2-4.5 g/m^2 + G-CSF
Feldman *et al*[153] 2010 (prospective phase I/II)	107	> 2 × 10^6/kg 100%	TI: paclitaxel 200 mg/m^2 d1 ifosfamide 2 g/m^2 d1-d3 + G-CSF
Haugnes *et al*[154] 2012 (prospective analysis)	882	> 2 × 10^6/kg 100%	BEP-ifosfamide + G-CSF
Mohr *et al*[155] 2012 (retrospective analysis)	44	> 4 × 10^6/kg 100%	PEI (cisplatin, etoposide, ifosfamide) + G-CSF Plerixafor in poor mobilizers
Necchi *et al*[156] 2015 (review)	42	> 2 × 10^6/kg 100%	BEP + G-CSF
Moeung *et al*[157] 2017 (pharmacokinetic phase II study)	89	> 9 × 10^6/kg (for 3 HDCT) (1-2 cycles) 100%	TI: paclitaxel, ifosfamide + G-CSF
Hamid *et al*[106] 2018 (retrospective analysis)	35	10/35 plerixafor + G-CSF 95%	TI: paclitaxel, ifosfamide or TIP
Argawal *et al*[158] 2019 (retrospective analysis)	321	172 allogeneic 95% 149 autologous 73% 77/149 without plerixafor → 64% success 72/149 with plerixafor → 82% success	G-CSF ± Plerixafor
Yildiz *et al*[159] 2020 (retrospective analysis)	50	> 2 × 10^6/kg 100%	TIP + G-CSF
Ussowicz *et al*[160] 2020 (retrospective analysis)	18 (children)	Median: 4.56 × 10^6/kg 100%	Cyclophosphamide 4 g/m^2 + G-CSF
Chevreau *et al*[161] 2020 (multicenter prospective phase II)	89	> 9 × 10^6/kg (for 3 HDCT) 100%	TI: paclitaxel, ifosfamide + G-CSF

G-CSF: Granulocyte colony-stimulating factor; HDCT: High-dose chemotherapy; TIP: Paclitaxel (Taxol)-ifosfamide-cisplatin.

Addition of mobilizing agents affecting a different pathophysiological pathway in order to improve peripheral stem cell collection

Ancestim: Ancestim is a recombinant human SCF that, through its binding to the c-kit receptor on HSCs, modulates their proliferation and adhesion, and has shown promising synergy in HSC mobilization when combined with G-CSF[119,120]. Limited efficacy when administered alone has also been noted[119]. Unfortunately, data available from recent studies did not confirm the efficiency in enhancing chemotherapy or growth factor-induced PBSC mobilization in patients with a prior insufficient PBSC collection, thus, limiting its further application[121].

GM-CSF: GM-CSF and its synergistic effect when combined with chemotherapy are no longer in use because the superiority of G-CSF in terms of mobilization and safety profile has been proved in a number of studies (*e.g.*, faster neutrophil recovery and fewer transfusions required)[122,123]. GM-CSF is sometimes used in combination with G-CSF in patients who failed an initial mobilization attempt, as a second or even as a third agent[124], despite the fact that several studies reported that the association of the two cytokines was not superior to G-CSF alone[125].

Plerixafor (Mozobil): Briefly, plerixafor was first studied as an agent against HIV [126]. During those clinical trials, neutrophilia was observed that sparked numerous studies[127]. In December 2008, plerixafor was approved by the Federal Drug Administration for use with G-CSF for HSC mobilization and collection and subsequent

ASCT in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM), who had failed prior mobilization with G-CSF alone or chemotherapy + G-CSF (plerixafor: AMD3100). The first report of the use of plerixafor in heavily pretreated, refractory and relapsed patients with GCTs was by Kobold *et al*[128]. Plerixafor was given subcutaneously in combination with G-CSF at a dose of 240 μg/kg after at least 4 d of G-CSF, which was given at the standard dose of 10 μg/kg/d. Plerixafor was administered 6 to 11 h before apheresis when a PB CD34+ count higher than 10/μL was achieved. The combination was successful, and allowed collection of sufficient numbers of CD34+ cells in 67% of the patients who failed prior mobilization with chemotherapy and G-CSF[128].

Despite the fact that the efficacy of plerixafor as a stem cell mobilization agent in patients with GCTs undergoing HDCT and ASCT has been reported in a number of small patient series and case studies, its use has not yet been approved, because of the lack of prospective studies. Thus, the indications for the use of plerixafor as a mobilization agent in patients with relapsed/refractory GCTs are not yet clear and rely on the opinions of the authors who published the studies (see Table 2 for details).

Structure and mechanism of action are as follows. Plerixafor (or AMD3100) is a bicyclam derivative that reversibly competes with and inhibits SDF-1a binding to CXCR4. CXCR4 is expressed on many cell types including white blood cells, epithelial, endothelial cells, and HPCs. It plays a critical role in the homing and trafficking of HPCs, as well as their retention and maintenance in the bone marrow niche. CXCR4 is a member of one of the two major families of chemokines. Chemokines are defined by the number and spacing of cysteine residues at the N-terminal end of the protein. CC cytokines have two cysteine residues that are adjacent; in CXC cytokines they separated by one amino-acid residue[129]. CXCR4 ligand, the chemokine SDF-1a (CXCL12), is produced by bone marrow stromal cells including osteoblasts, endothelial cells, and adventitial cells. Plerixafor was shown to directly inhibit SDF-1a ligand binding, SDF-1 mediated G-protein activation, calcium flux, and receptor internalization[130]. In another study, Lee *et al*[131] described the activation of phosphorylation of MAPK-p42/44 in granulocytes and monocytes by plerixafor, which induced the secretion of several proteases from the cells and enhanced the cleavage and activation of C5 in plasma. The C5 cleavage fragments (C5a and desArgC5a) play a critical role, as mentioned earlier, in the egress of HSCs. Granulocytes, stimulated and chemo-attracted by these fragments, enhance secretion of proteolytic enzymes that perturb HSCs retention signals and help HSCs to move through the endothelial barrier[131].

A possible mechanism for plerixafor-stimulated HSCs mobilization was proposed by Dar *et al*[132], in which an increase in CXCL12 circulating in the plasma was observed after the administration of plerixafor. At the same time, CXCL12 levels in BM fluids were decreased. The changes correlated with an increase of circulating progenitor cells in the blood, suggesting that SDF-1 actively regulated the number of circulating progenitor cells. Furthermore, the plasma levels of S1P, a potent chemoattractant for hematopoietic progenitors, was increased following AMD3100 administration[132].

The pharmacokinetics of plerixafor after subcutaneous injection show a peak plasma concentration within 30-60 min. Up to 58% of plerixafor is bound to plasma proteins, and it is eliminated by the urinary route with a half-life of 4 h. Similar increases in HSC levels are observed after multiple daily injections, suggesting no cumulative drug effect after consecutive injections[37,38]. An interesting fact about the timing of plerixafor injection and the mobilization of CD34+ was reported by Lefrere *et al*[38]. They found that in good mobilizers, the PB CD34 + count remained high for at least 12 h after G-CSF plus plerixafor administration[38]. In contrast, in poor mobilizers, precise monitoring of the PB CD34+ cell count was required, because the peak CD34+ cell count occurred 6-9 h after plerixafor injection[38]. It is essential to emphasize the significant decrease in CD34+ count that was observed in the patients 8-12 h after the injection, in order to determine the optimal timing of apheresis[38]. Regarding adverse effects, plerixafor is well tolerated, with rare reports of severe side effects, such as hypotension, dizziness, and thrombocytopenia. The most commonly observed adverse effects are diarrhea, nausea, and skin erythema at the injection site [38].

Future novel approaches: Most novel HSC mobilizing agents are initially tested in MM and NHL patients, and ASCT candidates. Successful application in that setting allows further testing in patients with relapsed/refractory GCTs and other solid tumors where HDCT and autografting are indicated at some point during the disease course. CXCR4 antagonists like plerixafor, emerged as potent agents to rescue "hard-

Table 2 Clinical studies applying plerixafor with granulocyte colony-stimulating factor ± chemotherapy for hematopoietic stem cells mobilization in patients with relapsed/refractory germ cell tumors

Ref.	Number of patients participating	Successful mobilization rates on previously failed chemotherapy + G-SCF driven mobilization (> 2 × 10^6)	Mobilization techniques
Kobold *et al*[128] 2011 (Retrospective analysis)	6	66.67% (4)	Chemo + G-CSF failed
			Plerixafor + G-CSF
Horwitz *et al*[162] 2012 (Retrospective analysis)	21	76% (17)	Chemo + G-CSF failed
			Plerixafor + G-CSF
Worel *et al*[163] 2012 (Retrospective analysis)	11	91% (10)	Plerixafor + G-CSF
Garcia-Escobar *et al*[164] 2014 (Case series)	5	80% (4)	Chemo + G-CSF failed
			Plerixafor + G-CSF
Kosmas *et al*[165] 2014 (Pilot study)	14 (3)	100% (3)	Chemo + G-CSF failed
			Chemo + Plerixafor + G-CSF
O'Hara *et al*[166] 2014 (Retrospective analysis)	9 (3)	100% (3)	Plerixafor + G-CSF

Related case studies: Saure *et al*[167], 2010; Tuffaha and Adel-Rahman[168], 2011; De Blasio *et al*[169], 2013; Miltiadous *et al*[170], 2017. G-CSF: Granulocyte colony-stimulating factor.

to-mobilize" patients with MM, NHL, GCTs, and some rare solid tumors. Research in that area has expanded with the development of novel CXCR4 inhibitors, such as motixafortide (BL-8040) and BKT140 (4F-benzoyl-TN14003), a 14-residue biostable synthetic peptide that binds CXCR4 with much greater affinity than plerixafor (84 nmol/L *vs* 4 nmol/L). An interim analysis of the phase 3 GENESIS trial of motixafortide *vs* placebo, both with G-CSF, for HSC mobilization in MM demonstrated an almost 4.9-fold increased efficacy in obtaining the primary endpoint of a target of 6.0 × 10^6 CD34+ cells/kg with up to two apheresis sessions and that 5.6-fold more patients achieved that target with one apheresis. Moreover, the motixafortide arm allowed 88.3% of patients to proceed to transplant, as opposed to 10.8% in the placebo arm [133]. Another peptide CXCR4 antagonist, a clinical stage compound balixafortide (POL6326) was evaluated in healthy volunteers and proved to be safe, well tolerated, and induced effective mobilization of HSCs at doses ≥ 1500 μg/kg and was predicted to yield an adequate collection of 4 × 10^6 CD34+ cells/kg in a single apheresis[134].

Another area of interest in HSC mobilization is the role of the sphingosine-1-phosphate/S1P receptor 1 (S1P/S1P1) axis, and studies in mice demonstrated an additional PB HSC mobilization benefit of S1P1 agonist (SEW2871) treatment in combination with a CXCR4 antagonist, but not human G-CSF[135]. However, that approach still remains experimental, with no apparent clinical testing so far.

Small molecule inhibitors of VLA-4 such as BIO5192 and monoclonal IgG4 antibodies (*e.g.*, natalizumab) bind to the a4 subunit of the a4β1 (VLA-4) integrin expressed on most leucocytes including CD34+ progenitor cells, inhibit the interaction of VLA4 primarily with VCAM-1 (CD106) on stromal cells, and secondarily with other ligands, including the segment-1 domain of fibronectin[136,137]. The interactions lead to increased HSCs in the blood. Therefore, their application has been proposed in patients with hematologic malignancies who are candidates for ASCT[138,139]. Unfortunately the clinical use of VLA-4 inhibitors is currently limited to multiple sclerosis and other inflammatory diseases.

Bortezomib (Velcade, PS-341) is a proteasome inhibitor that interferes with the activation of nuclear factor-kappa B (NFκB) by preventing proteasomal degradation of IκBa. VCAM-1 expression is upregulated by the VCAM-1 promoter. The latter is activated by binding to NFκB6. As proteasome inhibitors can indirectly inhibit transcription and expression of VCAM-1, and knowing the importance of the VCAM1-VLA4 interaction for HSC homing and mobilization, the application of proteasome

inhibitors as a mobilizer of HSC was proposed[140].

Hypoxia-inducible factor (HIF) prolyl hydroxylase (PHD) inhibitors, such as FG-4497, synergize with G-CSF and plerixafor to enhance mouse HSC mobilization. Deletion of the Hif1a gene weakens the effect[141]. A potential mechanism of FG-4497 proposed in recent studies includes stabilizing HIF-1a protein and increased VEGF-A secretion by BM macrophages[64,65]. FMS-like tyrosine kinase-3 Ligand (FLT3L) binds the FLT3 (CD135) receptor expressed on HSCs and induces proliferation, differentiation, development, and mobilization. Its efficacy has been shown either as a single agent, or in combination with other molecules mentioned above, such as IL-8 or G-CSF [142]. As chemokine-chemokine receptor axes are involved in retention of HSCs in the BM microenvironment, chemokine receptor agonists have been proposed as therapeutic agents to facilitate the mobilization process. The compounds include agonists of the CXCR4 receptor expressed on HSCs (*e.g.*, CTCE-0021 and ATI-2341)[143] or chemokines binding to chemokine receptors expressed on granulocytes and monocytes [*e.g.*, CXCL2, also known as the growth-related oncogene protein-beta (GRO-β) and its specific binding to the CXCR2 receptor; CCL3, also known as macrophage inflammatory protein-1α (MIP-1α); or CXCL8, also known as IL-8, could be used alone or in combination with other mobilizing agents like G-CSF or plerixafor (AMD3100)][144-146].

A novel mobilization strategy was developed and tested in mice through combined targeting of the chemokine receptor CXCR2 on granulocytes and VLA4 in HSCs. Treatment resulted in rapid and synergistic mobilization along with an enhanced recruitment of long-term repopulating of HSCs. That was achieved when a CXCR2 agonist, a truncated form of GRO-β; (tGRO-β) was administered in conjunction with a VLA4 inhibitor, leading to rapid and potent HSC mobilization, which represents an exciting potential strategy that warrants clinical development[147]. A G-CSF-free mobilization regimen using a tGRO-β compound, MGTA-145, which is a CXCR2 agonist, in combination with plerixafor was developed in the context of *in vivo* HSC transduction as a gene therapy approach in a mouse model of β-thalassemia[148]. The MGTA-145+plerixafor combination resulted in robust mobilization of HSCs. Importantly, compared with G-CSF + plerixafor, MGTA-145 + plerixafor led to significantly less leukocytosis and no elevation of serum interleukin-6 levels, and was thus likely to be less toxic[148]. However, the above regimen has not yet been tested for HSCs mobilization in neoplastic diseases. Therefore, evidence is accumulating that CXCR4 receptor agonists could be used with other agents as mobilizing drugs. In particular, they may provide an alternative for patients who are poor mobilizers.

CONCLUSION

Despite the fact that GCTs are currently considered as curable tumors, almost 30% of patients presenting with metastatic disease at diagnosis are likely to experience disease progression at some point. The use of HDCT and ASCT has been established as a salvage therapeutic option, but a number of patients fail to mobilize with conventional strategies. Such poor mobilizers endanger the safety of the procedure. Along with conventional mobilization strategies, such as G-CSF and chemo-mobilization, the use of newer mobilizing agents like plerixafor has emerged with promising results for this group of patients.

Algorithms to improve the efficiency of HSC mobilization, for example "just in time" and preemptive, aim to minimize failures, obtain the desired CD34+ HSCs dose for one or more transplants with the least apheresis sessions, and thus reduce overall healthcare costs, are urgently required. As novel HSC mobilizing agents are initially tested in preclinical experimental models and hematologic malignancies, such as NHL and MM, their application in solid tumors, candidates for ASCT, and in particular GCTs, is lagging behind.

Two axes responsible for HSC retention in the BM stroma that have been explored are the CXCR4-CXCL12 (SDF-1) and the VLA4 (α4/β1)-VCAM1 pathways. Novel inhibitors of those interactions have been evaluated, either alone or in combination with G-CSF, or with GRO-β/CXCR2 axis co-stimulation. Nevertheless, as studies in this area are limited, future investigation should concentrate on finding new agents or establishing proper mobilization algorithms to achieve an adequate CD34+ dose required for a successful ASCT.

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