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

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Author contributions: Porfyriou E and Letsa S collected and analyzed data, wrote, and approved the article; Kosmas C wrote parts of the original and made additions in the revised article, critically evaluated collected data, supervised the study, and corrected and approved the article; All authors read, approved, and agreed on submission of the final version of the article.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

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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 cell mobilization strategies (HSCs) collected from the peripheral blood, after appropriate pharmacologic mobilization, have been 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.

Citation: Porfyriou E, Letsa S, Kosmas C. Hematopoietic stem cell mobilization strategies to support high-dose chemotherapy: A focus on relapsed/refractory germ cell tumors. World J Clin Oncol 2021; 12(9): 746-766
URL: https://www.wjgnet.com/2218-4333/full/v12/i9/746.htm
DOI: https://dx.doi.org/10.5306/wjco.v12.i9.746

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 $2.0 \times 10^6$ 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.
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 x 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 ancestrim); 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-1α (SDF-1α; 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.
Mechanisms have been described to explain the mechanism of action of G-CSF. HPCs and mature neutrophilic granulocytes from the bone marrow are mobilized following the administration of G-CSF. CSFR signaling also mediates the mobilization of hematopoietic progenitor cells that have an impact on survival, migration, proliferation, and differentiation. Several intracellular signaling cascades occur, including the Jak/Stat/Socs, Ras/Raf/MEK-1, very late antigen-4 (VLA-4) on HSCs, and a transmembrane SCF that binds to c-kit (CD117) on HSCs. The endothelial sinusoidal niche is composed of endothelial cells that are nestin-bright (nestin+)-smooth muscle perivascular cells 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.

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 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.

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. 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. Depletion of the macrophages results in downregulation of VCAM1, SDF1a, and SCF expression that disrupts the normal niche functions. The percentage of adipocytes in the BM, derived from mesenchymal cells, increases with age, leading to a fatty marrow with limited cell proliferation ability.

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. Later, in 1985 Welte et al. purified human G-CSF. Nagata et al. in Japan and independently Souza et al. 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., where an observation of increasing neutrophil counts approximately 2 h after injection made. The following year, Duhrsen et al. 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.

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. 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. G-CSFR signaling also mediates the mobilization of hematopoietic progenitor cells (HPCs) and mature neutrophilic granulocytes from the bone marrow. Multiple mechanisms have been described to explain the mechanism of action of G-CSF.
Porfyriou E et al. HSC mobilization strategies in GCTs

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 mechanisms 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 endothem and sinusoid 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 osteodental 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 (SIP) into the circulation by red blood cells, endothelial cells, and activated platelets. SIP is a strong chemoattractant of HSCs, creating an enabling environment for proliferation in the plasma[92,93]. SIP increases in blood and decreases in BM during mobilization, inhibiting SDF1 through the p38/Akt/mTOR pathway[92]. Both SDF1 and SIP are regulated by specificity protein (SP)-1, which is thought to maintain a balance of their antagonistic effects. Several studies also suggest a role of the C5α 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 chemotherpay 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 expression 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/m², whereas high doses at 7 g/m² 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/m² on day 1 plus ifosfamide at 2 g/m²/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]   | 15                 | Median BM 51.49 × 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]       | 20                 | 2.5 × 10^6/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]  | 31                 | 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]       | 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]    | 37                 | 3-6 × 10^6/kg 100%                                                                   | ifosfamide 2-4.5 g/m^2 + G-CSF                                                       |
| Feldman et al[153]    | 107                | > 2 × 10^6/kg 100%                                                                   | TIP: paclitaxel 200 mg/m^2 d1 ifosfamide 2 g/m^2 d1-d3 + G-CSF                       |
| Haugnes et al[154]    | 882                | > 2 × 10^6/kg 100%                                                                   | BEP: ifosfamide + G-CSF                                                              |
| Mohr et al[155]       | 44                 | > 4 × 10^6/kg 100%                                                                   | PEI (cisplatin, etoposide, ifosfamide) + G-CSF Plerixafor in poor mobilizers          |
| Necchi et al[156]     | 42                 | > 2 × 10^6/kg 100%                                                                   | BEP + G-CSF                                                                         |
| Moeung et al[157]     | 89                 | > 9 × 10^6/kg (for 3 HDCT) (1-2 cycles) 100%                                           | TIP: paclitaxel, ifosfamide + G-CSF                                                  |
| Hamid et al[158]      | 35                 | 10/35 plerixafor + G-CSF 95%                                                          | TIP: paclitaxel, ifosfamide or TIP                                                   |
| Argawal et al[159]    | 321                | 172 allogeneic 95% |149 autologous 73% |174/149 without plerixafor → 64%成功72/149 with plerixafor → 82% success | G-CSF ± Plerixafor                                                                  |
| Yildiz et al[160]     | 50                 | > 2 × 10^6/kg 100%                                                                   | TIP + G-CSF                                                                         |
| Usowicz et al[161]    | 18 (children)      | Median: 4.56 × 10^6/kg 100%                                                         | Cyclophosphamide 4 g/m^2 + G-CSF                                                     |
| Chevreau et al[161]   | 89                 | > 9 × 10^6/kg (for 3 HDCT) 100%                                                       | TIP: 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 meditated 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 chemo-attractant 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 × 10⁶) | Mobilization techniques |
|------|---------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------|
| Kobold et al[128] 2011 (Retrospective analysis) | 6 | 66.67% (4) | Chemo + G-CSF failed, Plerixafor + G-CSF failed |
| 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 × 10⁶ 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 × 10⁶ 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 α4 subunit of the α4β1 (VLA-4) integrin expressed on most leukocytes 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 (NFkB) by preventing proteasomal degradation of IκBα. 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-1α 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.
REFERENCES

1 Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med* 2006; 354: 1813-1826 [PMID: 16641398 DOI: 10.1056/NEJMra052638]

2 Bortin MM. A compendium of reported human bone marrow transplants. *Transplantation* 1970; 9: 571-587 [PMID: 4911417 DOI: 10.1097/00007890-197006000-00006]

3 Abrahamsen JF, Stamnesf, Liseth K, Hervig T, Bruserud O. Large-volume leukapheresis yields more viable CD34+ cells and colony-forming units than normal-volume leukapheresis, especially in patients who mobilize low numbers of CD34+ cells. *Transfusion* 2005; 45: 248-253 [PMID: 15660835 DOI: 10.1111/j.1537-2995.2004.02410.x]

4 Bajanic I, Dubravicc K, Batinic D, Cepulic BG, Mazic S, Hren D, Nemet D, Labar B. Large volume leukapheresis: Efficacy and safety of processing patient's total blood volume six times. *Transfus Apher Sci* 2011; 44: 139-147 [PMID: 21320801 DOI: 10.1016/j.transci.2011.01.005]

5 Necchi A, Miceli R, Pedrazzoli P, Giannatempo P, Secondino S, Di Nicola M, Faré E, Raggi D, Magni M, Matteucci P, Longoni P, Milanesi M, Paternò E, Ravagnani F, Arienti F, Nicolai N, Salvioni R, Carlo-Stella C, Gianni AM. Predictors of CD34+ cell mobilization and collection in adult men with germ cell tumors: implications for the salvage treatment strategy. *Clin Gynecol Oncol* 2014; 12: 196-202.e1 [PMID: 24361054 DOI: 10.1016/j.cgeo.2013.11.021]

6 Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000; 50: 7-33 [PMID: 10735013 DOI: 10.3322/canjclin.50.1.7]

7 Parkin DM, Ferlay J, Curado MP, Bray F, Edwards B, Shin HR, Forman D. Fifty years of cancer incidence: CIS I-IX. *Int J Cancer* 2010; 127: 2918-2927 [PMID: 21351270 DOI: 10.1002/ijc.25517]

8 Horwich A, Shipley J, Huddart R. Testicular germ-cell cancer. *Lancet* 2006; 367: 754-765 [PMID: 16157276 DOI: 10.1016/S0140-6736(06)68305-0]

9 Nauman M, Leslie SW. Nonseminomatous Testicular Tumors. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [PMID: 33760513]

10 Vasdev N, Moon A, Thorpe AC. Classification, epidemiology and therapies for testicular germ cell tumours. *Int J Dev Biol* 2013; 57: 133-139 [PMID: 23784823 DOI: 10.1387/ijdb.130031nv]

11 Gilligan T, Lin DW, Aggarwal R, Chism D, Cost N, Derweesh IH, Moon A, Thorpe AC. Classification, epidemiology and therapies for testicular germ cell tumours. *Int J Dev Biol* 2013; 57: 133-139 [PMID: 23784823 DOI: 10.1387/ijdb.130031nv]

12 Combink of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol* 2005; 23: 6549-6555 [PMID: 16170162 DOI: 10.1200/jco.2005.19.638]

13 Kocher PJ Sr, Einhorn L, Williams SD. VP-16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. *J Clin Oncol* 1986; 4: 528-536 [PMID: 3633952 DOI: 10.1200/jco.1986.4.4.528]

14 Porrata LF, Adjei AA. The pharmacologic basis of high dose chemotherapy with haematopoietic stem cell support for solid tumours. *Br J Cancer* 2001; 85: 484-489 [PMID: 11506483 DOI: 10.1054/bjc.2001.1970]

15 Motzer RJ, Nichols CJ, Margolin KA, Bacik J, Richardson PG, Vogelzang NJ, Bajorin DF, Lara PN Jr, Einhorn L, Mazumdar M, Bosl GJ. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol* 2007; 25: 247-256 [PMID: 17235042 DOI: 10.1200/jco.2005.05.4528]

16 Einhorn LH, Williams SD, Charness A, Bramses MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med* 2007; 357: 340-348 [PMID: 17652649 DOI: 10.1056/NEJMoa067749]

17 Pico JL, Rosti G, Kramar A, Wandt H, Koza V, Salvioni R, Theodore C, Lelli G, Siegert W, Horwich A, Raggi D, Abrahamsen JF, Stamnesf, Liseth K, Hervig T, Bruserud O. Large-volume leukapheresis yields more viable CD34+ cells and colony-forming units than normal-volume leukapheresis, especially in patients who mobilize low numbers of CD34+ cells. *Transfusion* 2005; 45: 248-253 [PMID: 15660835 DOI: 10.1111/j.1537-2995.2004.02410.x]

18 Motzer RJ, Mazumdar M, Sheinfeld J, Bajorin DF, Macapinlac HA, Bains M, Reich L, Flombaum D, Yamoah K, Yamzon J, Johnson-Chilla A, Keller J, Pluchino LA. Testicular Cancer, Version 2021 [PMID: 33760513]

19 Copelan EA. The pharmacologic basis of high dose chemotherapy with haematopoietic stem cell support for solid tumours. *Br J Cancer* 2001; 85: 484-489 [PMID: 11506483 DOI: 10.1054/bjc.2001.1970]

20 Thorsby E. A short history of HLA. *Tissue Antigens* 2009; 74: 101-116 [PMID: 19523022 DOI: 10.1111/j.1399-0039.2009.01291.x]
Asssociated with the Need for Plerixafor But Not with the Collection Result.

Goldschmidt H, Wuchter P. Platelet Count before Peripheral Blood Stem Cell Mobilization Is
Baertsch MA

procedure.

Cavazzana-Calvo M, Micléa JM. A specific time course for mobilization of peripheral blood CD34+
Lefrère F

for mobilization of stem cells for transplantation in patients with multiple myeloma.
Gertz MA

normal individuals with granulocyte-colony-stimulating factor: donor experiences and the effects on
Stroncek DF

factor (filgrastim) mobilization and blood stem cell apheresis from normal donors, and analysis of
Champlin R, Körbling M. Clinical toxicity and laboratory effects of granulocyte-colony-stimulating
Anderlini P

factor (filgrastim) mobilization and blood stem cell apheresis from normal donors, and analysis of
Champlin R, Körbling M. Clinical toxicity and laboratory effects of granulocyte-colony-stimulating
Anderlini P

the source of hematopoietic stem cells matter? Körbling M

hematopoietic stem cells: The circuitous path to clinical gene therapy for fanconi anemia. Blood
Becker PS

large volume leukapheresis is efficient and safe even in small children up to 15 kg body weight.
Bojanic I

M. Mazic S, Rajic L, Jakovljie G, Stepan J, Cepulic BG. Large volume leukapheresis is efficient and safe even in small children up to 15 kg body weight. Blood Transfus 2017; 15: 85-92 [PMID: 27136428 DOI: 10.2450/2016.0151-15]

Goldman JM, Johnson SA, Catoovsky D, Wareham NJ, Galton DA. Autografting for chronic granulocytic leukemia. N Engl J Med 1981; 305: 760 [PMID: 10.1056/nejm198109173051216]

Körbling M, Dörken B, Ho AD, Pazzutto A, Hunstein W, Fliedner TM. Autologous transplantation of blood-derived hemopoietic stem cells after myeloablative therapy in a patient with Burkitt's lymphoma. Blood 1986; 67: 529-532 [PMID: 2867797 DOI: 10.1182/blood.V67.2.529.bloodjournal672529]

Kessinger A, Armitage JO, Landmark JD, Weisenburger DD. Reconstitution of human hematopoietic function with autologous cryopreserved circulating stem cells. Exp Hematol 1986; 14: 192-196 [PMID: 2868909]

Thomas ED, Storb R. Technique for human marrow grafting. Blood 1970; 36: 507-515 [PMID: 4916990 DOI: 10.1182/blood.V36.4.507.507]

Becker PS, Adair J, Choi G, Lee A, Kiern HP. From bone marrow to mobilized peripheral blood stem cells: The circuitous path to clinical gene therapy for fanconi anemia. Blood 2018; 132 (Supple 1): 2208 [DOI: 10.1182/blood-2018-99-120278]

Körbling M, Anderlini P. Peripheral blood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cells matter? Blood 2001; 98: 2900-2908 [PMID: 11698269 DOI: 10.1182/blood.v98.e2900]

Stroncek DF, Dittmar K, Shawker T, Heatherman A, Leitman SF. Transient spleen enlargement in peripheral blood progenitor cell donors given G-CSF. J Transl Med 2004; 2: 25 [PMID: 15268759 DOI: 10.1186/1479-5876-2-25]

Körbling M, Freireich EJ. Twenty-five years of peripheral blood stem cell transplantation. Blood 2011; 117: 6411-6416 [PMID: 21460243 DOI: 10.1182/blood-2010-12-322214]

Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. International Society of Hemotherapy and Graft Engineering. J Hematother 1996; 5: 213-226 [PMID: 8817388 DOI: 10.1089/scl.1.1996.5.213]

Baertsch MA, Schlenzka J, Lisenko K, Krzykalla J, Becker N, Weisel K, Noppeney R, Martin H, Lindemann HW, Haenel M, Nogai A, Scheid C, Salwender H, Fenk R, Graeven U, Reimer P, Schmidt-Hieber M, Goerner M, Schmidt-Wolf IGH, Klein S, Ho AD, Goldschmidt H, Wuchter P. Cyclophosphamide-based stem cell mobilization in relapsed multiple myeloma patients: A subgroup analysis from the phase III trial Rel.ApsE. Eur J Haematol 2017; 99: 42-50 [PMID: 28370401 DOI: 10.1111/ej.12888]

Nowrousian MR, Waschke S, Bojko P, Welt A, Schuett P, Ebeling P, Flaschowe M, Moritz T, Schuette J, Seeber S. Impact of chemotheraphy regimen and hematopoietic growth factor on mobilization and collection of peripheral blood stem cells in cancer patients. Ann Oncol 2003; 14 Suppl 1: i29-i36 [PMID: 12736228 DOI: 10.1093/annonc/mdg706]

Anderlini P, Przepiorka D, Seong D, Miller P, Sundberg J, Lichtiger B, Norfleet F, Chan KW, Champlin R, Körbling M. Clinical toxicity and laboratory effects of granulocyte-colony-stimulating factor (filgrastim) mobilization and blood stem cell apheresis from normal donors, and analysis of charges for the procedures. Transfusion 1996; 36: 590-595 [PMID: 8701453 DOI: 10.1046/j.1537-2995.1996.36796323057.x]

Stroncek DF, Clay ME, Petzoldt ML, Smith J, Jaszes W, Oldham FB, McCullough J. Treatment of normal individuals with granulocyte-colony-stimulating factor: donor experiences and the effects on peripheral blood CD34+ cell counts and on the collection of peripheral blood stem cells. Transfusion 1996; 36: 601-610 [PMID: 8701455 DOI: 10.1046/j.1537-2995.1996.36796323059.x]

Kriegsmann K, Schmitt A, Kriegsmann M, Bruckner T, Anyanwu A, Witzens-Harig M, Müller-Tidow C, Klein S, Wuchter P. Orchestration of Chemomobilization and G-CSF Administration for Successful Hematopoietic Stem Cell Collection. Biol Blood Marrow Transplant 2018; 24: 1281-1288 [PMID: 29353110 DOI: 10.1016/j.bbmt.2018.01.007]

Gertz MA, Kumar SK, Lacy MQ, Dispenzieri A, Hayman SR, Buadi FK, Dingli D, Gastineau DA, Winters JL, Litzow MR. Comparison of high-dose CY and growth factor with growth factor alone for mobilization of stem cells for transplantation in patients with multiple myeloma. Bone Marrow Transplant 2009; 43: 619-625 [PMID: 18997825 DOI: 10.1038/bmt.2008.369]

Kessans MR, Gatesman ML, Koekler DR. Plerixafor: a peripheral blood stem cell mobilizer. Pharmacotherapy 2010; 30: 485-492 [PMID: 20411999 DOI: 10.1592/phco.30.5.485]

Lefrère F, Mauge L, Résa D, Ribeil JA, Dal Cortivo L, Brignier AC, Aoun C, Larghéro J, Cavazzana-Calvo M, Micléa JM. A specific time course for mobilization of peripheral blood CD34+ cells after plerixafor injection in very poor mobilizer patients: impact on the timing of the apheresis procedure. Transfusion 2013; 53: 564-569 [PMID: 22725259 DOI: 10.1111/j.1537-2995.2012.03744.x]

Baertsch MA, Kriegsmann K, Pavel P, Bruckner T, Hundemer M, Kriegsmann M, Ho AD, Goldschmidt H, Wuchter P. Platelet Count before Peripheral Blood Stem Cell Mobilization Is Associated with the Need for Plerixafor But Not with the Collection Result. Transfus Med Hemother 2018; 45: 24-31 [PMID: 29593457 DOI: 10.1159/000478911]

Hsu YM, Cushing MM. Autologous Stem Cell Mobilization and Collection. Hematol Oncol Clin North Am 2016; 30: 573-589 [PMID: 27112997 DOI: 10.1016/j.hoc.2016.01.004]
Porfyriou E et al. HSC mobilization strategies in GCTs

41 Teng HW, Hsiao LT, Chauo SC, Gau JP, Lee TC, Shih YY, Liu CY, Hong YC, Chen MH, Chang MH, Yang YH, Chen PM. A new model for predicting the timing of leukapheresis on the basis of CD34+ cell and hematopoietic progenitor cell levels. J Clin Apher 2007; 22: 195-203 [PMID: 17294459 DOI: 10.1002/jca.20117]

42 Wood WA, White J, Moore D, Sharp A, Irons R, Rao K, Serody J, Coghill J, Gabriel D, Shea T. 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 [PMID: 20637882 DOI: 10.1016/j.bbmt.2010.06.021]

43 Costa LJ, Nista EJ, Buadi FK, Lacy MQ, Dispenzieri A, Kramer CP, Edwards KH, Kang Y, Gertz MA, Stuart RK, Kumar S. Prediction of poor mobilization of autologous CD34+ cells with growth factor in multiple myeloma patients: implications for risk-stratification. Biol Blood Marrow Transplant 2014; 20: 222-228 [PMID: 24211319 DOI: 10.1016/j.bbmt.2013.11.003]

44 Giralt S, Costa L, Schrier J, Dipersio J, Mazzar J, McCarty J, Shaughnessy P, Snyder E, Bensinger W, Copelan E, Hosing C, Negrin R, Petersen FB, Rondelli D, Soiffer R, Leather H, Pazzalia A, Devine S. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014; 20: 295-308 [PMID: 24141007 DOI: 10.1016/j.bbmt.2013.10.013]

45 Schofield R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood Cells 1978; 4: 7-25 [PMID: 747780]

46 Doetsch F, Caillé I, Lim DA, García-Verdujo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 1999; 97: 703-716 [PMID: 10380923 DOI: 10.1016/s0009-8884(98)00783-7]

47 Kimble JE, White JG. On the control of germ cell development in Caenorhabditis elegans. Dev Biol 1981; 81: 208-219 [PMID: 7208337 DOI: 10.1016/0012-1606(81)90284-0]

48 Nilsson SK, Johnson JM, Coverdale JA. Spatial localization of transplanted hematopoietic stem cells: inferences for the localization of stem cell niches. Blood 2001; 97: 2293-2299 [PMID: 11290590 DOI: 10.1182/blood.v97.8.2299]

49 Quiñones-Hinojosa A, Sanai N, Soriano-Navarro M, Gonzalez-Perez O, Mirzadeh Z, Gil-Peotin S, Romero-Rodriguez R, Berger MS, Garcia-Verdujo JM, Alvarez-Buylla A. Cellular composition and cytoarchitecture of the adult human subventricular zone: a niche of neural stem cells. J Comp Neurol 2006; 494: 415-434 [PMID: 1630258 DOI: 10.1002/cne.20798]

50 Wilson A, Oser GM, Jaworski M, Blanco-Bose WE, Laurenti E, Adolphc C, Essers MA, Macdonald HR, Trumppe A. Dormant and self-renewing hematopoietic stem cells and their niches. Ann N Y Acad Sci 2007; 1106: 64-75 [PMID: 17442778 DOI: 10.1196/annals.1392.021]

51 Kopp HG, Aveccilla ST, Hooper AT, Raffi S. The bone marrow vascular niche: home of HSC differentiation and mobilization. Physiology (Bethesda) 2005; 20: 349-356 [PMID: 16174874 DOI: 10.1152/physiol.00005.2005]

52 Zhu J, Garrett R, Jung Y, Zhang Y, Kim N, Wang J, Joe GJ, Huxner E, Choi Y, Taichman RS, Emerson SG. Osteoblasts support B-lymphocyte commitment and differentiation from hematopoietic stem cells. Blood 2007; 109: 3706-3712 [PMID: 17227831 DOI: 10.1182/blood-2006-08-041384]

53 Zhu CH, Xie T. Clonal expansion of ovarian germ line stem cells during niche formation in Drosophila. Development 2003; 130: 2579-2588 [PMID: 12782030 DOI: 10.1242/dev.00499]

54 Eliasson P, Jönsson J. The hematopoietic stem cell niche: low in oxygen but a nice place to be. J Cell Physiol 2010; 222: 17-22 [PMID: 19725055 DOI: 10.1002/jcp.21908]

55 Mohyeldin A, Garzón-Muvdi T, Quiñones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. Cell Stem Cell 2010; 7: 150-161 [PMID: 20682444 DOI: 10.1016/j.stem.2010.07.007]

56 Zhang CC, Sadek HA. Hypoxia and metabolic properties of hematopoietic stem cells. Antioxid Redox Signal 2014; 20: 1891-1901 [PMID: 23621582 DOI: 10.1089/ars.2012.5019]

57 Panvini FM, Pacini S, Montali M, Barachini S, Mazzoni S, Morganti R, Ciancia EM, Carnicelli V, Petrini M. High NESTIN Expression Marks the Endosteal Capillary Network in Human Bone Marrow. Front Cell Dev Biol 2020; 8: 596452 [PMID: 33364234 DOI: 10.3389/fcell.2020.596452]

58 Boulaís PE, Frenette PS. Making sense of hematopoietic stem cell niches. Blood 2015; 125: 2621-2629 [PMID: 25762174 DOI: 10.1182/blood-2014-09-570192]

59 Kunisaki Y, Bruns I, Scheiermann C, Ahmed J, Pinho S, Zhang D, Mizoguchi T, Wei Q, Lucas D, Ito K, Mar JC, Bergman A, Frenette PS. Arteriolar niches maintain haematopoietic stem cell quiescence. Nature 2013; 502: 637-643 [PMID: 24107994 DOI: 10.1038/nature12612]

60 Mendelsohn A, Frenette PS. Hematopoietic stem cell niche maintenance during homeostasis and regeneration. Nat Med 2014; 20: 833-846 [PMID: 25100529 DOI: 10.1038/nm.3647]

61 Bleul CC, Fulhügge RC, Casasnovas JM, Aiuti A, Springer TA. A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1). J Exp Med 1996; 184: 1101-1109 [PMID: 9064327 DOI: 10.1084/jem.184.3.1101]

62 Papayannopoulou T, Craddock C, Nakamoto B, Priestley GV, Wolf NS. The VLA4/VCAM-1 adhesion pathway defines contrasting mechanisms of lodgement of transplanted murine hematopoietic progenitors between bone marrow and spleen. Proc Natl Acad Sci USA 1995; 92: 9647-9651 [PMID: 7568190 DOI: 10.1073/pnas.92.21.9647]

63 Lennartsson J, Rönnstrand L. Stem cell factor receptor/c-Kit: from basic science to clinical implications. Physiol Rev 2012; 92: 1619-1649 [PMID: 23073628 DOI: 10.1152/physrev.00046.2011]
mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. Petit I [PMID: 10.1016/j.cytogfr.2014.07.011] Lévesque JP 1134 [PMID: 10.1007/978-1-61779-943-3_1 principles and molecular mechanisms. Bonig H cyclophosphamide. Lévesque JP Exp Med 2011; 208: 261-271 [PMID: 21282381 DOI: 10.1016/j.exphem.2010.07.002] Christopher MJ, Link DC. Granulocyte colony-stimulating factor induces osteoblast apoptosis and inhibits osteoblast differentiation. J Bone Miner Res 2008; 23: 1765-1774 [PMID: 18597629 DOI: 10.1038/jbmr.080612] Link DC. Mechanisms of granulocyte colony-stimulating factor-induced hematopoietic progenitor cell mobilization. Semin Hematol 2000; 37: 25-32 [PMID: 10718150 DOI: 10.1053/shem.1999.00866-6] Christopher MJ, Rao M, Liu F, Woloszynek JR, Link DC. Expression of the G-CSF receptor in mononuclear cells is sufficient to mediate hematopoietic progenitor mobilization by G-CSF in mice. J Exp Med 2011; 208: 251-260 [PMID: 21282380 DOI: 10.1016/j.exphem.2010.07.002] Lévesque JP, Hendy J, Takamatsu Y, Simmons PJ. Mobilization by either cyclophosphamide or granulocyte colony-stimulating factor transforms the bone marrow into a highly proteolytic environment. Exp Hematol 2002; 30: 440-449 [PMID: 12031650 DOI: 10.1016/s0301-472x(02)00788-9] Christopherson KW, Cooper S, Hanceg G, Brommeyer HE. CD26 is essential for normal G-CSF-induced progenitor cell mobilization as determined by CD26−/− mice. Exp Hematol 2003; 31: 1126-1134 [PMID: 14858379 DOI: 10.1016/j.exphem.2003.07.002] Lévesque JP, Hendy J, Takamatsu Y, Simmons PJ, Bendall LJ. Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide. J Clin Invest 2003; 111: 187-196 [PMID: 12331874 DOI: 10.1172/jci15994] Bonig H, Papayannopoulou T. Mobilization of hematopoietic stem/progenitor cells: general principles and molecular mechanisms. Methods Mol Biol 2012; 904: 1-14 [PMID: 22890918 DOI: 10.1007/978-1-61779-943-3_1] Bendall LJ, Bradstock KF. G-CSF: From granulopoietic stimulant to bone marrow stem cell mobilizing agonist. Cytokine Growth Factor Rev 2014; 25: 355-367 [PMID: 25131807 DOI: 10.1016/j.cytogfr.2014.07.011] Lévesque JP, Takamatsu Y, Nilsson SK, Haylock DN, Simmons PJ. Vascular cell adhesion molecule-1 (CD106) is cleaved by neutrophil proteases in the bone marrow following hematopoietic progenitor cell mobilization by granulocyte colony-stimulating factor. Blood 2001; 98: 1289-1297 [PMID: 11520773 DOI: 10.1182/blood.v98.5.1289] Petit I, Szyper-Kravitz M, Nagler A, Lahav M, Peled A, Habler L, Ponomaryov T, Taichman RS, Arenzana-Seisdedos F, Fuji N, Sandbank J, Zipori D, Ladipot T. G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. Nat Immunol 2002; 3: 687-694 [PMID: 12068293 DOI: 10.1038/nm813]
followed by stem cell rescue for high-risk germ cell tumors: the Stanford experience.

Bendall LJ, Sims NA, Lévesque JP. Hematopoietic stem cell mobilizing agents G-CSF, cyclophosphamide or AMD3100 have distinct mechanisms of action on bone marrow HSC niches

Kanda J, McClune B, Shaughnessy P, Tricot GJ, Chao NJ. Outcomes and costs of autologous stem cell mobilization with chemotherapy plus G-CSF

Moura R, Giorgio M, Pelicci P, Avogaro A, Fadini GP. Diabetes causes bone marrow autonomic neuropathy and impairs stem cell mobilization

Massalha H, Bernshtein B, Ciechanowicz AK, Brandis A, Mehlman T, Bhattacharya S, Bertagna M, Rzeszotek S, García-García A, Xie S, Flores-Figueroa E, Gur-Cohen S, Itkin T, Ludin-Tal A, Méndez-Ferrer S, Vagima Y, Ludin A, Itkin T, Cohen-Gur S, Kalinkovich A, Kollet O, Kim C, Schajnovitz, T, Lazarini F, Virelizier JL, Chignard M, Pidard D, Arenzana-Seisdedos F. Leukocyte elastase 25749109, Itoh Y, Chiba T, Mori H, Okada A, Kinoh H, Seiki M. Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration. J Cell Biol 2001; 153: 893-904 [PMID: 11381077 DOI: 10.1083/jcb.153.5.893]

Semerad CL, Christopher MJ, Liu F, Short B, Simmons PJ, Winkler I, Levesque JP, Chappell J, Ross FP, Link DC. G-CSF potently inhibits osteoblast activity and CXCL12 mRNA expression in the bone marrow. Blood 2005; 106: 3020-3027 [PMID: 16037394 DOI: 10.1182/blood-2004-01-0272]

Lévesque JP, Helwani FM, Winkler IG. The endostea 'osteoblastic' niche and its role in hematopoietic stem cell homing and mobilization. Leukemia 2010; 24: 1979-1992 [PMID: 20861913 DOI: 10.1038/leu.2010.214]

Katayama Y, Battista M, Kao WM, Hidalgo A, Peirèd AJ, Thomas SA, Frenette PS. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. Cell 2006; 124: 407-421 [PMID: 16439213 DOI: 10.1016/j.cell.2005.10.041]

Takamatsu Y, Simmons PJ, Moore RJ, Morris HA, To LB, Lévesque JP. Osteoclast-mediated bone resorption is stimulated during short-term administration of granulocyte colony-stimulating factor but is not responsible for hematopoietic progenitor cell mobilization. Blood 1998; 92: 3465-3473 [PMID: 9787169 DOI: 10.1182/blood.V92.9.3465.3473]

Golan K, Vagima Y, Ludin A, Itkin T, Cohen-Gur S, Kalinkovich A, Kollet O, Kim C, Schajnovitz A, Odvay A, Lapid K, Shvitriel S, Morris AJ, Rajacjazk MZ, Lapidot T. SIP promotes murine progenitor cell egress and mobilization via SIP1-mediated ROS signaling and SDF-1 release. Blood 2012; 119: 2478-2488 [PMID: 22279055 DOI: 10.1182/blood-2011-06-358614]

Ratajczak MZ, Lee H, Wysoczynski M, Wan W, Marlicz W, Laughlin MJ, Kucia M, Janowska-Wieczorek A, Rajacjazk J. Novel insight into stem cell mobilization-plasma sphingosine-1-phosphate is a major chemoattractant that directs the egress of hematopoietic stem progenitor cells from the bone marrow and its level in peripheral blood increases during mobilization due to activation of complement cascade/membrane attack complex. Leukemia 2010; 24: 976-985 [PMID: 20357827 DOI: 10.1038/leu.2010.53]

Reca R, Cramer D, Yan J, Laughlin MJ, Janowska-Wieczorek A, Rajacjazk J, Rajacjazk MZ. A novel role of complement in mobilization: immunodeficient mice are poor granulocyte-colony stimulating factor mobilizers because they lack complement-activating immunoglobulins. Stem Cells 2007; 25: 3093-3100 [PMID: 17717064 DOI: 10.1634/stemcells.2007-0525]

Méndez-Ferrer S, Lucas D, Battista M, Frenette PS. Haematopoietic stem cell population is regulated by circadian oscillations. Nature 2008; 452: 442-447 [PMID: 18256599 DOI: 10.1038/nature06685]

Golan K, Kumari A, Kollet O, Khatri-Massalha E, Subramaniam MD, Ferreira ZS, Avemaria F, Rzeszotek S, Garcia-Garcia A, Xie S, Flores-Figureso E, Gur-Cohen S, Itkin T, Ludin-Tal A, Massalha H, Bernshtein B, Ciechanowicz AK, Brandis A, Mehlin T, Bhattacharya S, Bertagna M, Cheng H, Petrovich-Kopftman E, Janus T, Kaushansky N, Cheng T, Sagi I, Rajacjazk MZ, Méndez-Ferrer S, Dick JE, Markus RP, Lapidot T. Daily Onset of Light and Darkness Differentially Controls Hematopoietic Stem Cell Differentiation and Maintenance. Cell Stem Cell 2018; 23: 572-585.e7 [PMID: 30174297 DOI: 10.1016/j.stem.2018.08.002]

Albiero M, Poncina N, Tiwa M, Ciciliot S, Menegazzo L, Ceolotto V, Vigili de Kreutzberg S, Mora R, Giorio M, Pelicci P, Avogaro A, Fadini GP. Diabetes causes bone marrow autonomic neuropathy and impairs stem cell mobilization via dysregulated p66Shc and Sirt1. Diabetes 2014; 63: 1353-1365 [PMID: 24270983 DOI: 10.2337/db13-0894]

Fadini GP, Albiero M, Vigili de Kreutzberg S, Boscare O, Cappellari R, Mariscotti M, Poncina N, Agostini C, Avogaro A. Diabetes impairs stem cell and proangiogenic cell mobilization in humans. Diabetes Care 2013; 36: 943-949 [PMID: 23111057 DOI: 10.2337/dc12-1084]

Sung AD, Grima DT, Bernard LM, Brown S, Carrum G, Holmberg I, Horwitz ME, Liesveld JL, Kanda J, McClune B, Shaughnessy P, Tricot GJ, Chao NJ. Outcomes and costs of autologous stem cell mobilization with chemotherapy plus G-CSF vs G-CSF alone. Bone Marrow Transplant 2013; 48: 1444-1449 [PMID: 23749109 DOI: 10.1038/bmt.2013.80]

Lévesque JP, Hendy J, Winkler IG, Takamatsu Y, Simmons PJ. Granulocyte colony-stimulating factor induces the release in the bone marrow of proteases that cleave c-KIT receptor (CD117) from the surface of hematopoietic progenitor cells. Exp Hematol 2003; 31: 109-117 [PMID: 12591275 DOI: 10.1016/s0301-472x(02)01028-7]

Winkler IG, Pettit AR, Raggatt LJ, Jacobsen RN, Forristal CE, Barbier V, Nowlan B, Cisterne A, Bendall LJ, Sims NA, Lévesque JP. Hematopoietic stem cell mobilizing agents G-CSF, cyclophosphamide or AMD3100 have distinct mechanisms of action on bone marrow HSC niches and bone formation. Leukemia 2012; 26: 1594-1601 [PMID: 22266913 DOI: 10.1038/leu.2012.17]

Agarwal R, Dvorak CC, Stockert-Goldstein KE, Johnston L, Srinivas S. High-dose chemotherapy followed by stem cell rescue for high-risk germ cell tumors: the Stanford experience. Bone Marrow
Hübel K, Haas R, Kobbe G. A single dose of 6 or 12 mg of pegfilgrastim for peripheral blood progenitors in malignant lymphoma patients candidate for high-dose chemotherapy. *J Clin Oncol* 1998; 16: 2601-2612 [PMID: 9704709 DOI: 10.1200/jco.1998.16.8.2601]

Rieck O, Schwella N, Beyer J, Dubiel M, Krusch A, Hildebrandt M, Schleicher J, Serke S, Siegert W. PBPC mobilization with paclitaxel, ifosfamide, and G-CSF with or without amifostine: results of a prospective randomized trial. *Transfusion* 2001; 41: 196-200 [PMID: 11239222 DOI: 10.1046/j.1537-2995.2001.41020196.x]

Feldman DR, Powlis T. Salvage high-dose chemotherapy for germ cell tumors. *Urol Oncol* 2015; 33: 355-362 [PMID: 25837842 DOI: 10.1016/j.urolonc.2015.01.025]

Hamid AA, Markt SC, Vicier C, McDermott K, Richardson P, Ho VT, Sweeney CJ. Autologous Stem-Cell Transplantation Outcomes for Relapsed Metastatic Germ-Cell Tumors in the Modern Era. *Clin Genitourin Cancer* 2019; 17: 58-64 [e1] [PMID: 30309761 DOI: 10.1016/j.clgc.2018.09.009]

André M, Baudoux E, Bron D, Canon JL, D'Hondt V, Fassotte MF, D'Hondt L, Fillet G, Humbert Y, Jerusalem G, Vermeulen P, Symann M, Beger U. Phase III randomized study comparing 5 or 10 microg per kg per day of filgrastim for mobilization of peripheral blood progenitor cells with chemotherapy, following by intensification and autologous transplantation in patients with nonmyeloid malignancies. *Transfusion* 2003; 43: 50-57 [PMID: 12519430 DOI: 10.1046/j.1537-2995.2003.00273.x]

Demirer T, Ayli M, Ozcan M, Guzel N, Hafizoglu I, Dagli M, Deniz O, Gürkan G, Demirer S, Güneş E, Usal A, Konuk N, Ilhan O, Koc H, Akça A. Mobilization of peripheral blood stem cells with chemotherapy and recombinant human granulocyte colony-stimulating factor (rhG-CSF): a randomized evaluation of different doses of rhG-CSF. *Br J Haematol* 2002; 116: 468-474 [PMID: 11841454 DOI: 10.1046/j.1365-2411.2002.03264.x]

Kim S, Kim HJ, Park JS, Lee J, Chi HS, Park CJ, Huh J, Suh C. Comparative randomized prospective 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 [PMID: 16132903 DOI: 10.1007/s00277-005-1103-8]

Oh-eda M, Hasegawa M, Hattori K, Kuboniwa H, Kojima T, Orita T, Tomonou K, Yamazaki T, Ochi N. O-linked sugar chain of human granulocyte colony-stimulating factor protects it against polymerization and denaturation allowing it to retain its biological activity. *J Biol Chem* 1990; 265: 11432-11435 [PMID: 1694845 DOI: 10.1016/S0021-9258(98)93416-9]

Pedrazzoli P, Gibelli N, Pavesi L, Preti P, Piolini M, Bertolini F, Robustelli della Cunha G. Effects of glycosylated and non-glycosylated G-CSFs, alone and in combination with other cytokines, on the growth of human progenitor cells. *Anticancer Res* 1996; 16: 1781-1785 [PMID: 8712701]

Kopf B, De Giorgi U, Vertogen B, Monti G, Molinari A, Tursi D, Dazzi C, Leoni M, Tenghi A, Cariello A, Argmann M, Frassineti L, Scarpi E, Rosti G, Marangolo M. A randomized study comparing filgrastim versus lenograstim versus molgramostim plus chemotherapy for peripheral blood progenitor cell mobilization. *Bone Marrow Transplant* 2006; 38: 407-412 [PMID: 16931690 DOI: 10.1038/sj.bmj.17105465]

Böning H, Silbermann S, Soller S, Kirschke R, Höhfeld M, Dossian G, Göbel U, Nürnberg W. Glycosylated vs non-glycosylated granulocyte colony-stimulating factor (G-CSF)--results of a prospective randomised monocentre study. *Bone Marrow Transplant* 2001; 28: 259-264 [PMID: 11535993 DOI: 10.1038/sj.bmj.1703136]

Sourgens H, Lefrère F. A systematic review of available clinical evidence - filgrastim compared with lenograstim. *Int J Clin Pharmacol Ther* 2011; 49: 510-518 [PMID: 21781651 DOI: 10.4414/cp201537]

Molineux G, Kinstler O, Bridelll B, Hartley C, McElroy P, Kerzic P, Sutherland W, Stoney G, Kern B, Fletcher FA, Cohen A, Korach E, Ulrich T, McNeece I, Lockbaum P, Miller-Messana MA, Gardiner S, Hunt T, Schwab G. A new form of Filgrastim with sustained duration in vivo and enhanced ability to mobilize PBPC in both mice and humans. *Exp Hematol* 1999; 27: 1724-1734 [PMID: 10641590 DOI: 10.1016/s0301-472x(99)00112-5]

Putkonen M, Raahala A, Pellineni TT, Remes K. Single-dose pegfilgrastim is comparable to daily filgrastim in mobilizing peripheral blood stem cells: a case-matched study in patients with lymphoproliferative malignancies. *Ann Hematol* 2009; 88: 673-680 [PMID: 19139894 DOI: 10.1007/s00277-008-0675-5]

Bassi S, Rabascio C, Nasi L, Steffanoni S, Babic A, Bertazzoni P, Gigli F, Antoniotti P, Orlando L, Sammussino S, Quarna J, Negri M, Martinelli G. 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. *Transfus Apher Sci* 2010; 43: 321-326 [PMID: 21036667 DOI: 10.1016/j.transci.2010.10.001]

Brums I, Steidl U, Kronenwett R, Fenk R, Graef T, Rohr UP, Neumann F, Fischer J, Scheid C, Hübel K, Haas R, Kobbe G. A single dose of 6 or 12 mg of pegfilgrastim for peripheral blood progenitor cell mobilization results in similar yields of CD34+ progenitors in patients with multiple myeloma. *Transfusion* 2006; 46: 180-185 [PMID: 16441592 DOI: 10.1111/j.1537-2995.2006.00699.x]
Porfyriou E et al. HSC mobilization strategies in GCTs

Marty J, Rawling T, Ashman L, Charles S, Cohen B. Successful mobilization of peripheral blood stem cells after addition of anestim (stem cell factor) in patients who had failed a prior mobilization with filgrastim (granulocyte-colony-stimulating factor) alone or with chemotherapy plus filgrastim. Bone Marrow Transplant 2003; 31: 371-378 [PMID: 12634728 DOI: 10.1038/sj.bmt.1703860]

Broadwell RA, Hartley CA, Smith KA, McNiece I. Recombinant rat stem cell factor synergizes with recombinant human granulocyte-colony-stimulating factor in vivo to mobilize peripheral blood progenitor cells that have enhanced repopulating potential. Blood 1995; 82: 1720-1723 [PMID: 7691233 DOI: 10.1182/blood.V82.6.1720.bloodjournal8261720]

da Silva MG, Pimentel P, Carvalhais A, Barbosa I, Machado A, Campilho F, Sousa SR, Miranda N, da Costa FL, Campos A, Vaz CP, Antas J, Passos-Coelho JL. Anestim (recombinant human stem cell factor, SCF) in association with filgrastim does not enhance chemotherapy and/or growth factor-induced peripheral blood progenitor cell (PBPC) mobilization in patients with a prior sufficient PBPC collection. Bone Marrow Transplant 2004; 34: 683-691 [PMID: 15322567 DOI: 10.1038/sj.bmt.1704602]

Peters WP, Rosner G, Ross M, Vredenburgh J, Meisenberg B, Gilbert C, Kurtzberg J. 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 [PMID: 7681699 DOI: 10.1182/blood.V81.7.1709.bloodjournal8171709]

Lane TA, Law P, Maruyama M, Young D, Burgess J, Mullens M, Mealiffe M, Terstappen LW, Hardwick A, Moubyad M. 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 [PMID: 7528570 DOI: 10.1182/blood.V85.1.275.bloodjournal851275]

Bot FJ, van Eijk L, Schipper P, Backx B, Löwenberg B. Synergistic effects between GM-CSF and G-CSF or M-CSF on highly enriched human marrow progenitor cells. Leukemia 1990; 4: 325-328 [PMID: 1697008]

Spitzer G, Adkins D, Mathews M, Velasquez W, Bowers C, Dunphy F, Kronmueller N, Niemeyer R, McIntyre W, Petruska P. Randomized comparison of G-CSF + GM-CSF (GM-CSF) or G-CSF: potential role in allogeneic marrow transplantation. Blood 2006; 1053-1056 [PMID: 16932485 DOI: 10.1016/S0188-6673(06)63173-1]

Leukemia 2010; 24: 573-582 [PMID: 20033053 DOI: 10.1038/leu.2009.271]

Creech JD, Stockel-Goldstein K, Vainstein A, Chen H, DiPersio JF. GENESIS: Phase III trial evaluating BL-8040 + G-CSF to mobilize hematopoietic progenitors for autologous transplant in myeloma. Future Oncol 2019; 15: 3555-3563 [PMID: 31495201 DOI: 10.2217/fon-2019-0380]

Karpova D, Bräuningner S, Wiercinska E, Krämer A, Stock B, Graff J, Martin H, Wach A, Escot C, Douglas G, Romagnoli B, Chevalier E, Dembowski K, Hoofman L, Bonig H. Mobilization of hematopoietic stem cells with the novel CXCR4 antagonist POL6326 (balixafortide) in healthy volunteers-results of a dose escalation trial. J Transl Med 2017; 15: 2 [PMID: 28049490 DOI: 10.1186/s12967-016-1107-2]

Cleary LF, Stockel-Goldstein K, Vainstein A, Chen H, DiPersio JF. GENESIS: Phase III trial evaluating BL-8040 + G-CSF to mobilize hematopoietic progenitors for autologous transplant in myeloma. Future Oncol 2019; 15: 3555-3563 [PMID: 31495201 DOI: 10.2217/fon-2019-0380]

Karpova D, Bräuningner S, Wiercinska E, Krämer A, Stock B, Graff J, Martin H, Wach A, Escot C, Douglas G, Romagnoli B, Chevalier E, Dembowski K, Hoofman L, Bonig H. Mobilization of hematopoietic stem cells with the novel CXCR4 antagonist POL6326 (balixafortide) in healthy volunteers-results of a dose escalation trial. J Transl Med 2017; 15: 2 [PMID: 28049490 DOI: 10.1186/s12967-016-1107-2]
primates and mice. *Blood* 1997; 90: 4779-4788 [PMID: 9389694]

137 **Bonnig H**, Watts KL, Chang KH, Kiem HP, Papayannopoulou T. Concurrent blockade of alpha4-integrin and CXCR4 in hematopoietic stem/progenitor cell mobilization. *Stem Cells* 2009; 27: 836-837 [PMID: 19350684 DOI: 10.1002/stem.9]

138 **Ramirez P**, Rettig MP, Uy GL, DeCyh E, Holt MS, Ritschy JK, DiPersio JF. BDF05192, a small molecule inhibitor of VLA-4, mobilizes hematopoietic stem and progenitor cells. *Blood* 2009; 114: 1340-1343 [PMID: 19571319 DOI: 10.1182/blood-2008-10-184721]

139 **Rettig MP**, Anastass G, DiPersio JF. Mobilization of hematopoietic stem and progenitor cells using inhibitors of CXCR4 and VLA-4. *Leukemia* 2012; 26: 34-53 [PMID: 21886173 DOI: 10.1038/leu.2011.197]

140 **Ghobadi A**, Fiala MA, Rettig M, Schroeder M, Uy GL, Stockerl-Goldstein K, Westervelt P, Vij R, DiPersio JF. A Phase I Study of the Safety and Feasibility of Bortezomib in Combination With G-CSF for Stem Cell Mobilization in Patients With Multiple Myeloma. *Clin Lymphoma Myeloma Leukemia* 2019; 19: e588-e593 [PMID: 31558485 DOI: 10.1016/j.clml.2019.04.017]

141 **Forristal CE**, Nowlan B, Jacobsen RN, Barbier V, Walkinshaw G, Walkley CR, Winkler IG, Levesque JP. HIF-1α is required for hematopoietic stem cell mobilization and 4-prolyl hydroxylase inhibitors enhance mobilization by stabilizing HIF-1α. *Leukemia* 2015; 29: 1366-1378 [PMID: 25578474 DOI: 10.1038/leu.2015.8]

142 **He S**, Chu J, Vasi S, Deng Y, Yuan S, Zhang J, Fan Z, Hofmeister CC, He X, Marsh HC, Devine SM, Yu J. FLT3L and plerixafor combination increases hematopoietic stem cell mobilization and leads to improved transplantation outcome. *Biol Blood Marrow Transplant* 2014; 20: 309-313 [PMID: 24365795 DOI: 10.1016/j.bbmt.2013.11.024]

143 **Ratajczak MZ**, Kim C. The use of chemokine receptor agonists in stem cell mobilization. *Expert Opin Biol Ther* 2012; 12: 287-297 [PMID: 22203752 DOI: 10.1517/14712598.2012.671747]

144 **Pelas LM**, Fukuda S. Peripheral blood stem cell mobilization: the CXCR2 ligand GRObeta rapidly mobilizes hematopoietic stem cells with enhanced engraftment properties. *Exp Hematol* 2006; 34: 1010-1020 [PMID: 16863907 DOI: 10.1016/j.exphem.2006.04.004]

145 **Nevi B**, Link DC, DiPersio JF. Cytokines and hematopoietic stem cell mobilization. *J Cell Biochem* 2006; 99: 690-705 [PMID: 16888804 DOI: 10.1002/jcb.21043]

146 **Ha H**, Debnath B, Neamati N. Role of the CXCL8-CXCR1/2 Axis in Cancer and Inflammatory Diseases. *Theranostics* 2017; 7: 1543-1588 [PMID: 28529637 DOI: 10.7150/thno.15625]

147 **Karpova D**, Rettig MP, Ritchey J, Cancilla D, Christ S, Gehrs L, Chandamairi E, Evbuomwan MO, Holt M, Zhang J, Abou-Ezzii G, Celik H, Wiercinska E, Yang W, Gao F, Eisenberg LG, Heier RF, Arnett SD, Meyers MJ, Prinsen MJ, Griggs DW, Trumpa A, Runinski PG, Morrow DM, Bonig HB, Link DC, DiPersio JF. Targeting VLA4 integrin and CXCR2 mobilizes serially repopulating hematopoietic stem cells. *J Clin Invest* 2019; 129: 2745-2759 [PMID: 31085833 DOI: 10.1172/JCI124738]

148 **Li C**, Goncalves KA, Raskó T, Pande A, Gil S, Liu Z, Izsák Z, Papayannopoulou T, Davis JC, Gorincour G, Krabbe K, Aakre E, Debnath B, Neamati N. Role of the CXCL8-CXCR1/2 Axis in Cancer and Inflammatory Diseases. *Theranostics* 2017; 7: 1543-1588 [PMID: 28529637 DOI: 10.7150/thno.15625]

149 **Fruehauf S**, Haas R, Conradt C, Murea S, Witt B, Möhle R, Hunstein W. Peripheral blood progenitor cell (PBPC) counts during steady-state hematopoiesis allow to estimate the yield of mobilized PBPC after filgrastim (R-metHuG-CSF)-supported cytotoxic chemotherapy. *Exp Hematol* 2006; 34: 2619-2626 [PMID: 17537123 DOI: 10.1182/blood.v85.9.2619.bloodjournal8592619]

150 **Tada T**, Takizawa T, Nakazato F, Kobayashi S, Koike K, Oguchi M, Ishii E, Amano Y. Treatment of intracranial nongerminomatous germ-cell tumor by high-dose chemotherapy and autologous stem-cell rescue. *J Neurooncol* 1999; 44: 71-76 [PMID: 10582672 DOI: 10.1023/a:1006395719917]

151 **Rodenhuis S**, de Wit R, de Mulder PH, Sleijfer DT, Lalisiang RI, Bakker PJ, Mandjes I, Kool M, de Vries EG. A multi-center prospective phase II study of high-dose chemotherapy in germ-cell cancer patients relapsing from complete remission. *Ann Oncol* 1999; 10: 1467-1473 [PMID: 10643538 DOI: 10.1016/a.00832802102040]

152 **Lotz JP**, Bui G, Bussière MT, Théodore C, Caty A, Fizzari K, Gravis G, Delva R, Peny J, Viens P, Duclos B, De Revel T, Curé H, Gligorov J, Guillaumot S, Ségura C, Provent S, Droz JP, Culine S, Binet P, Groupe d’Etudes des Tumeurs Uro-Génitales (GETUG). Sequential high-dose chemotherapy protocol for relapsed poor prognosis germ cell tumors combining two mobilization and cytoreductive treatments followed by three high-dose chemotherapy regimens supported by autologous stem cell transplantation. Results of the phase II multicentric TAXIL trial. *Ann Oncol* 2005; 16: 411-418 [PMID: 15659420 DOI: 10.1093/annonc/mdl087]

153 **Feldman DR**, Sheinfeld J, Bajorin DF, Fischer P, Turkula S, Isshill N, Patel S, Bains M, Reich LM, Boldt GJ, Motzer RJ. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. *J Clin Oncol* 2010; 28: 1706-1713 [PMID: 20194867 DOI: 10.1200/JCO.2009.25.1561]

154 **Haunges HS**, Laurell A, Stierne U, Brennes RM, Dahl O, Cavallin-Stålhl E, Cohn-Cedermark G. High-dose chemotherapy with autologous stem cell support in patients with metastatic non-seminomatous testicular cancer - a report from the Swedish Norwegian Testicular Cancer Group (SWENOTECA). *Acta Oncol* 2012; 51: 168-176 [PMID: 22175254 DOI: 10.3109/0284186X.2011.645107]

155 **Mohr M**, Hartig I, Kessler T, Hamisch C, Klinesh C, Krug U, Spiekter T, Semik M, Wiebe K, Pühlse
Porfyriou E et al. HSC mobilization strategies in GCTs

G, Herte L, Liersch R, Müller-Tidow C, Mesters RM, Berdel WE. High-dose chemotherapy with autologous PBSC transplantation for poor prognosis germ cell tumors: a retrospective monocenter analysis of 44 cases. Bone Marrow Transplant 2012; 47: 1321-1325 [PMID: 22327136 DOI: 10.1036/bmt.2012.14]

Necchi A, Lanza F, Rosi G, Martino M, Faré E, Pedrazzoli P. European Society for Blood and Marrow Transplantation, Solid Tumors Working Party (EBMT-STWP) and the Italian Germ Cell Cancer Group (IGG). High-dose chemotherapy for germ cell tumors: do we have a model? Expert Opin Biol Ther 2015; 15: 33-44 [PMID: 25243977 DOI: 10.1517/14712598.2015.963051]

Moeung S, Chevreau C, Brouin S, Guitton J, Lelièvre B, Ciccolini J, Massart C, Fléchon A, Delva R, Gravis G, Lotz JP, Bay JO, Gross-Goupil M, Paci A, Marsili S, Malard L, Chatelut E, Thomas F. Therapeutic Drug Monitoring of Carboplatin in High-Dose Protocol (TI-CE) for Advanced Germ Cell Tumors: Pharmacokinetic Results of a Phase II Multicenter Study. Clin Cancer Res 2017; 23: 7171-7179 [PMID: 28928162 DOI: 10.1159/000784322.CCR-17-1344]

Agrawal P, Teijwani N, Pathak A, Kumar D, Agrawal N, Mehta A. Benefits of Pre-harvest Peripheral Blood CD34 Counts Guided Single Dose Therapy with PLERIXAFOR in Autologous Hematopoietic Stem Cell Transplantation: A Retrospective Study at a Tertiary Care Institute in India. Indian J Hematol Blood Transfus 2019; 35: 72-76 [PMID: 30828151 DOI: 10.1007/s12288-018-0979-0]

Vildiz F, Durmali A, Erselan E, Ilhan A, Tufan G, Aslan F, Arslan UY, Alkis N, Demirci U, Altuntas F, Oksuşoğlu B. Outcomes of Autologous Stem Cell Transplantation (ASCT) in Relapsed/Refractory Germ Cell Tumors: Single Center Experience from Turkey. Urol J 2020; 17: 497-500 [PMID: 32569258 DOI: 10.22037/uj.v16i7.6004]

Ussowicz M, Mielcarek-Siedziuk M, Musial J, Stachowiak M, Węcławek-Tompol J, Sęga-Pondel D, Frazzkiewicz T, Trefiliska J, Raciborska A, Melphalan, Etoposide, and Carboplatin Megatherapy with Autologous Stem Cell Transplantation in Children with Relapsing or Therapy-Resistant Extracranial Germ-Cell Tumors-A Retrospective Analysis. Cancers (Basel) 2020; 12: 33352733 DOI: 10.3390/cancers12123841

Chevreau C, Massard C, Flechon A, Delva R, Gravis G, Lotz JP, Bay JO, Gross-Goupil M, Fizazi K, Mourey L, Paci A, Guitton J, Thomas F, Lelièvre B, Ciccolini J, Moeung S, Gallois Y, Olivier P, Cuîne S, Filleron T, Chatelut E. Multicentric phase II trial of TI-CE high-dose chemotherapy with therapeutic drug monitoring of carboplatin in patients with relapsed advanced germ cell tumors. Cancer Med 2021; 10: 2250-2258 [PMID: 33675184 DOI: 10.1002/cam4.3687]

Horwitz ME, Long G, Holman P, Libby E, Calandra GC, Schirber JR. Efficacy and safety of hematopoietic stem cell remobilization with plerixafor+G-CSF in adult patients with germ cell tumors. Bone Marrow Transplant 2012; 47: 1283-1286 [PMID: 22343676 DOI: 10.1038/bmt.2012.21]

Worel N, Apperley JF, Basak GW, Douglas KW, Gabriel IH, Gerudels C, Hübel K, Jaksic O, Koristek Z, Lanza F, Lemoli R, Mikula G, Selleslag D, Duarte RF, Mohty M. European data on stem cell mobilization with plerixafor in patients with non-hematologic diseases: an analysis of the European consortium of stem cell mobilization. Transfusion 2012; 52: 2395-2400 [PMID: 22414093 DOI: 10.1111/j.1537-2995.2012.03603.x]

García-Escobar I, Parrilla L, Ortega LM, Castellanos D, Pallarès MA, Cortés-Funés H. Clinical experience with plerixafor as a mobilization regimen for autologous peripheral blood stem cell transplantation in patients with refractory germ cell tumors. Mol Clin Oncol 2014; 2: 923-926 [PMID: 25279175 DOI: 10.3892/mco.2014.162]

Kosmas C, Athanasopoulos A, Dimitriadias G, Miliadous C, Zilakos M, Lydakis D, Magiorkinis E, Athanasopoulos A, Dimitriadis G, Roditis P, Kosmas C. Plerixafor mobilization of peripheral blood CD34+ cells guided by a single dose of plerixafor in a patient with a germ cell tumor. Acta Haematol 2010; 124: 235-238 [PMID: 20999212 DOI: 10.1111/j.1159-1021.2010.00215.x]

Tuffaha H, Abdel-Rahman FA. Successful stem-cell mobilization and transplantation using plerixafor in a patient with a germ cell tumor. Hematol Oncol Stem Cell Ther 2010; 3: 203-205 [PMID: 21150242 DOI: 10.1016/j.hemonc.2010.02.003]

De Blasio A, Rossi L, Zappone E, Ortu La Barbera E, Salvatorti R, Pacilli M, Carbone A, Zaccarelli E, Papa A, Tomao S. Plerixafor and autologous stem cell transplantation: impressive result in a chemoresistant testicular cancer patient treated with high-dose chemotherapy. Anticancer Drugs 2013; 24: 653-657 [PMID: 23698254 DOI: 10.1097/CAD.0b013e328360c8dc]

Miliadous C, Dimitriadias GK, Roditis P, Kosmas C. Plerixafor mobilization of peripheral blood hematopoietic progenitors to support further high-dose chemotherapy cycles in a patient with germ-cell tumor relapsing after previous tandem high-dose chemotherapy and hematopoietic cell transplantation: report of a case. Anticancer Drugs 2017; 28: 237-241 [PMID: 27749622 DOI: 10.1097/CAD.0000000000000444]
