Mobilization of Hematopoietic Stem Cells for Use in Autologous Transplantation

Hollie Devine, MSN, RN, CNP, D. Kathryn Tierney, RN, PhD, Kim Schmit-Pokorny, RN, MSN, OCN®, and Kathleen McDermott, RN, BSN, OCN®

Autologous hematopoietic stem cell transplantation (HSCT) is a potentially curative therapeutic approach for various malignant hematologic and lymphoid diseases. Hematopoietic stem cells (HSCs) may be collected from the blood or the bone marrow. HSCs are capable of self-renewal and give rise to progenitor cells, multipotent cells that differentiate and proliferate into the mature cells of the blood and immune system. HSCs and progenitor cells are released from the bone marrow into the peripheral blood through a process called mobilization. HSCs then are collected from the blood in a process called apheresis and cryopreserved for administration following the high-dose preparative regimen. This article reviews stem cell biology, current mobilization strategies, use of novel mobilization agents, and nursing care of patients during the mobilization phase of autologous HSCT. Understanding the biology and process of HSC mobilization is critical for transplantation nurses to deliver and coordinate care during this complex phase of autologous HSCT.

At a Glance

- Mobilization of hematopoietic stem cells (HSCs) from the bone marrow into the peripheral blood is a multistep process involving the interplay among chemokines, cytokines, cell adhesion molecules, and the bone marrow microenvironment.
- The goal of stem cell collection is to mobilize a sufficient number of HSCs that are capable of regenerating the full hematopoietic lineages and to achieve adequate engraftment following autologous HSC transplantation.
- Nurses need to understand stem cell biology and the mechanisms of action of current mobilization strategies.

Autologous hematopoietic stem cell transplantation (HSCT) is a therapeutic approach that is potentially curative for a number of malignant hematologic and lymphoid diseases. The three types of HSCT are allogeneic, autologous, and syngeneic. In allogeneic transplantation, the hematopoietic stem cells (HSCs) are obtained from a human leukocyte antigen–matched sibling, an unrelated volunteer donor, or cryopreserved umbilical cord blood. In autologous HSCT, the HSCs are collected from the bone marrow or the blood of the patient when the cancer is in remission or a state of minimal residual disease. The third type of HCT is a syngeneic transplantation, where the source of the graft is an identical twin. Peripheral blood HSCs have largely replaced the use of bone marrow as the graft source for autologous HSCT. The benefits of using HSCs collected from the blood compared to HSCs collected from the bone marrow include a shorter period of neutropenia, which translates into reduced use of antibiotics, decreased risk of infection, shorter hospitalization, and reduced costs (Schmitz et al., 1996; Smith et al., 1997).

The focus of this article is the mobilization of HSCs for use in autologous HSCT. The term mobilization is used to describe the process by which HSCs are released from the bone marrow into the blood. The biology of HSCs and the mechanisms by which HSCs remain in the bone marrow microenvironment or are released into the blood will be reviewed. To date, the two principle means of mobilization are the use of cytokines alone or the use of cytokines in combination with chemotherapy. These mobilization strategies will be described. Strategies for individuals who do not collect a sufficient graft with current mobilization techniques will be reviewed, including the use of novel mobilization agents. The collection, processing, and cryopreservation of HSCs will be outlined.

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Digital Object Identifier: 10.1188/10.CJON.212-222
The Hematopoietic System

Hematopoiesis is a cell-renewal process that leads to the constant manufacturing of functional differentiated blood cells from HSCs and progenitor cells (Lataillelade, Domenech, & Le Bourse-Kerdiles, 2004). HSCs are cells that can differentiate into functional mature blood cells while maintaining an indefinite capacity for self-renewal. HSCs have three general properties: they are capable of self-renewing, they are unspecialized, and they give rise to specialized cells. HSCs are vital in that they assist in regenerating cells damaged by disease, injury, and daily use (Stem Cell Information, 2006). A progenitor cell is a dividing cell with capacity to differentiate. The developmental pathway of HSCs into functional blood cells involves loss of the potential to proliferate, with progressive differentiation into specific blood elements with defined functions. These fully differentiated blood cells have finite life spans, requiring constant renewal from the HSC pool (Manz, Akashi, & Weissman, 2004).

In the bone marrow microenvironment, stem cells may remain quiescent for long periods of time until they are activated for the purpose of homeostasis or tissue repair (Manz et al., 2004). Inside the bone marrow reside long-term HSCs that have the capacity for self-renewal (see Figure 1). A subset of these long-term HSCs will differentiate into short-term HSCs, which give rise to multipotent progenitors of either the myeloid or lymphoid cell lineages. The common lymphoid progenitor differentiates into precursors of the B and T lymphocyte and natural killer lineages. The common myeloid progenitor gives rise to two types of progenitors; the granulocyte-monocyte progenitor and a megakaryocyte-erythrocyte progenitor. The granulocyte-monocyte progenitor produces the granulocyte lineages (which produce neutrophils, basophils, and eosinophils), the monocyte-macrophage lineages, and the dendritic cell lineages. The megakaryocyte-erythrocyte progenitor produces the erythroid-lineage cells and megakaryocytes (Manz et al., 2004).

Table 1 describes the function of each blood cell.

<table>
<thead>
<tr>
<th>Blood Cell Type</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>Transport oxygen and carbon dioxide</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>Phagocytosis, chemotaxis, and storage of granules</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Phagocytosis, immune response, tissue repair</td>
</tr>
<tr>
<td>Platelets</td>
<td>Blood clotting</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Immune response</td>
</tr>
</tbody>
</table>

Stem Cell Biology

As HSCs mature, they express specific combinations of cell surface proteins that serve as biochemical markers. These biochemical markers identify the evolutionary stage of the blood cell, dictate the next steps in cell maturation, and serve as regulatory signals (Scholssman et al., 1997; Zola et al., 2003, 2005, 2007). Flow cytometry through the use of fluorescent-labeled antibodies is a technique for analyzing multiple markers of individual cells. The cluster of differentiation or cluster of designation (CD) system is the nomenclature used to classify and analyze cell surface molecules present on leukocytes. The CD marker is used to associate cells with certain immune functions and properties (Scholssman et al., 1997; Zola et al., 2003, 2005, 2007). CD34 is a marker of HSCs and is used clinically to separate HSCs from other types of leukocytes (see Figure 2). As HSCs differentiate, they lose the CD34 marker and acquire other biochemical markers specific to a lineage. T cells will acquire CD4 or CD8 surface markers and B cells will acquire surface immunoglobulin markers and antigen-specific receptors (Manz et al., 2004).

Bone Marrow Microenvironment

Inside the bone marrow is a multifunctional network of cells and extracellular matrix that maintain HSC proliferation, differentiation, and survival. This network of cells and extracellular matrix are known as the bone marrow microenvironment (see Figure 3). Stromal cells are the layers of cells that support the infrastructure of the bone marrow. Stromal cells assist in the regulation of HSCs and are important cells for providing differentiation signals to HSCs. Additionally, stromal cells direct the movement of HSCs out of the bone marrow and into the peripheral circulation (Lataillelade et al., 2004). Stromal cells produce stromal-cell-derived factor-1α (SDF-1α), a chemokine widely expressed by many tissues such as the ectoderm, endoderm, mesoderm, and mesenchymal cells (McGrath, Koniski, Malby, McGann, & Palis, 1999). SDF-1α is a signaling molecule involved in the proliferation, homing, and engraftment of HSCs and leukocytes.

Mechanisms of Mobilization

In addition to HSCs and stromal cells, mobilization of HSCs from the bone marrow into the peripheral blood is a multistep process involving interplay between chemokines, cytokines, and cell adhesion molecules (CAMs). Chemokines are small proteins that regulate cellular movement (Laing & Secombes, 2004). Chemokines are produced by hematopoietic and non-hematopoietic cells, including leukocytes, platelets, stromal cells, the gastrointestinal tract, ovary, prostate,
thymus, heart, and spleen (Broxmeyer & Kim, 1999). Chemokines induce the migration of cells to sites of infection or injury, activate an immune response, stimulate wound healing, and direct the movement of myeloid progenitor cells (Broxmeyer & Kim, 1999; Laing & Secombes, 2004).

Cytokines are intracellular signaling proteins that have autocrine, paracrine, and endocrine functions (Cannon, 2000). Their role is to facilitate communications among immune system cells. Cytokines function locally or at a distance to enhance immunity; act by binding to their cell-specific receptors, which are located on the cell membrane; and regulate the innate immune system (i.e., natural killer cells, macrophages, and neutrophils). They also regulate the adaptive immune system and T- and B-cell immune responses (Anderson, 1999). Other cytokine functions include inflammatory reactions, wound healing, and formation of blood cells.

Multiple chemokines may bind to a single receptor whereas cytokines are activated by interactions with a unique and specific ligand (Lataillade et al., 2004). CXCR4 is a chemokine receptor that is expressed on dendritic, endothelial, neural cells and on mature blood cells (Lataillade et al., 2004). HSCs express CXCR4 for a given time in their development. When binding of CXCR4 to SDF-1α occurs, activation of integrins and CAMs direct the movement of HSCs along the stromal cell membrane (Lataillade et al., 2004). Integrins are receptors for cell adhesion to extracellular matrix proteins and play an important role in cell-to-cell adhesion. Integrins and their ligands are instrumental in cell development, immune responses, leukocyte trafficking, and homeostasis (Hynes, 2002). CAMs are glycoproteins present on the external surface of the cell membrane. They recognize and interact either with other CAMs on adjacent cells or with proteins of the extracellular matrix. The adhesion of CXCR4 to SDF-1α induces the arrest of HSCs, allowing HSCs to migrate toward a local gradient of SDF-1α. The final anchoring of HSCs within the bone marrow microenvironment is maintained by the continuous production of SDF-1α by stromal cells. The loss of attachment to the stromal cells along with the loss of SDF-1α activity releases HSCs into the peripheral circulation (Lataillade et al., 2004).

Cytokines also have an integral role in HSC trafficking, including both the proliferation and expansion of HSCs. Granulocyte–colony-stimulating factor (G-CSF) allows for the release of HSCs from the bone marrow through secondary interactions with stromal cells, chemokine receptor interactions, and the degradation of integrins (Lapidot & Petit, 2002). The release of proteases cleave vascular cell adhesion molecule-1 and very late antigen-4, which are CAMs expressed on stromal cells. In steady state, CAMs bind to SDF-1α, anchoring HSCs to the stromal cells within the bone marrow. Administration of G-CSF degrades vascular cell adhesion molecule-1, resulting in the release of HSCs into circulation (Lapidot & Petit, 2002).

Another mechanism by which stem cell mobilization occurs is through chemokine antagonists. Chemokine antagonists (AMD3100) block the CXCR4 receptor located on the surface of each HSC. By blocking the CXCR4 receptor, inhibition of the binding of SDF-1α occurs, allowing HSCs to be released from the bone marrow and into the circulating blood.

### Current Mobilization Strategies

As previously described, mobilization is a method of stimulating HSCs that originate in the bone marrow to increase in number and move into the peripheral blood. The goals of mobilization are to move a sufficient number of HSCs that are capable of regenerating the full hematopoietic lineages and to achieve adequate engraftment following autologous HSCT. Adequate engraftment generally is defined as achieving an absolute neutrophil count greater than 0.5 x 10^9/L in 10–12 days and a platelet count greater than 20 x 10^9/L in 15–30 days. An ideal mobilization regimen results in the collection of sufficient HSCs leading to rapid and durable engraftment, a low toxicity profile, and a minimal number of apheresis procedures (Pusic et al., 2008). The collection goal is based on a predetermined number of CD34+ cells/kg of body weight. A minimum of 2 x 10^6 CD34+ cells/kg is a collection goal cited often in the literature (Koc et al., 2000; Pusic et al., 2008). A higher number of CD34 cells present in the graft correlates with more rapid engraftment of both neutrophils and platelets (Bensinger et al., 1995; Pusic et al., 2008; Vogel et al., 1998). Current mobilization strategies include the use of cytokines alone or cytokines combined with myelosuppressive chemotherapy.
Two U.S. Food and Drug Administration (FDA)-approved cytokines for mobilization are G-CSF (filgrastim) and granulocyte macrophage-colony-stimulating factor (GM-CSF) (sargramostim). To date, G-CSF is the cytokine most commonly used for mobilization (Bensinger, DiPersio, & McCarty, 2009). One of the earliest studies to assess the effect of GM-CSF on the number of HSCs in the peripheral blood was reported by Socinski et al. (1988). The authors concluded that administration of GM-CSF with or without chemotherapy increased the number of colony-forming unit-granulocyte macrophage (CFU-GM) in peripheral blood and may facilitate the collection of HSCs for use in autologous HSCT. In the time since Socinski et al. (1988) was published, many studies have explored the use of cytokines for HSC mobilization. In aggregate, these studies have shown that both G-CSF and GM-CSF facilitate adequate collections of HSCs for use in autologous HSCT in the majority of patients (Bishop et al., 1994; Nademanee et al., 1994; Weaver et al., 2000). G-CSF alone as a mobilization agent yields better CD34+ cell collections than GM-CSF alone (Gazitt, 2002; Weaver et al., 2000).

G-CSF is administered as a subcutaneous injection, and patients can be taught self-administration. A typical regimen is to administer the G-CSF for four days and begin apheresis on the fifth day of G-CSF (Pusic et al., 2008). Administration of G-CSF continues until the desired CD34+ cell dose is collected.

Limitations exist to mobilization of HSCs with cytokines. Common side effects include bone pain, fever, and malaise. Less commonly noted side effects include chills, headache, nausea, vomiting, diarrhea, edema, rash, dyspnea, pleural or pericardial effusion, and nasal congestion (Schmit-Pokorny, 2004). Rare side effects that have been reported include splenic rupture and pneumothorax (Becker et al., 1997).

Chemotherapy and Cytokines

A second strategy for mobilizing HSCs is to combine myelosuppressive chemotherapy with a cytokine. Chemotherapy agents used for mobilization include cyclophosphamide, etoposide, paclitaxel, and cytarabine (Bensinger et al., 2009; Tarella et al., 2002). In some cases, disease-specific chemotherapy, such as DHAP (etoposide, cytosine arabinoside, methylprednisolone, and cisplatin) in patients with lymphoma, may be combined with G-CSF for mobilization.

One of the first observations that HSCs increased in the peripheral blood after chemotherapy administration was reported by Richman, Weiner, and Yankee (1976). Following administration of myelosuppressive chemotherapy, a proliferation occurs of both HSCs and progenitor cells in the bone marrow, resulting in some of these cells migrating into the circulation (Ng-Cashin, 2004). The number of HSCs and progenitor cells released into the peripheral blood after chemotherapy can be enhanced by the addition of cytokines.

An early study on the use of cyclophosphamide to mobilize HSCs reported a 14-fold increase in CFU-GM about 17 days following cyclophosphamide administration (To et al., 1990). Since the publication of To et al. (1990), numerous studies have examined different combinations of chemotherapy and cytokines, different doses of either the chemotherapy or the cytokines, and different schedules of chemotherapy and cytokines. Table 3 shows results from several trials. The use of myelosuppressive chemotherapy in combination with a cytokine for mobilization has been shown to result in improved CD34+ cell yields over cytokines alone (Bensinger et al., 1995, 2009; Pusic et al., 2008).

Other benefits of the combination of chemotherapy and cytokines may be a reduced number of apheresis procedures and more rapid engraftment related to a higher number of CD34+ cells collected. In turn, more rapid engraftment can reduce the length of hospitalization, reduce the risk of infection, and reduce the number of transfusions. Another potential benefit may be a reduced risk of tumor cell contamination of the graft; however, whether this translates into a reduced risk of relapse has been debated (Bensinger et al., 2009).

Several disadvantages exist when chemotherapy is added to the mobilization regimen. One possible disadvantage is the need for hospitalization to administer the chemotherapy. Secondly, the patient is exposed to the side effects and toxicities associated with the chemotherapeutic agent. Of significant concern is the subsequent period of neutropenia and the associated risk of infection. One study reported that 30% of patients mobilized...
with chemotherapy plus cytokine were hospitalized for neutropenic fever, 39% required transfusions of red blood cells, and 30% required transfusions of platelets (Koc et al., 2000). The variability in the time to the recovery of the white blood cells following myelosuppressive chemotherapy leads to challenges in scheduling apheresis.

The current mobilization strategies, cytokines alone or cytokines combined with myelosuppressive chemotherapy, have advantages and disadvantages. One disadvantage of both mobilization strategies is the risk of an insufficient collection of HSCs to proceed to autologous HSCT. In one retrospective review of 1,040 patients who received either G-CSF alone or G-CSF in combination with myelosuppressive chemotherapy, about 19% in each group were unable to collect a sufficient number of CD34+ cells (Pusic et al., 2008). Selecting a mobilization strategy will be based on multiple variables that may include the research or treatment protocol, institutional practices, and the underlying disease.

### Poor Mobilizers

Poor mobilization often is defined as collection of less than 1–2 x 10^6 CD34+ cells/kg (Goterris et al., 2005; Haas et al., 1994; Kessinger & Sharp, 2003; Stiff, 1999). Various factors have been associated with poor mobilization, including specific types or amounts of chemotherapy, patients older than 60 years, and prior pelvic radiation. Patients who do not collect enough HSCs may not proceed to transplantation; the risks of using a suboptimal HSC collection are delayed, partial, or failed engraftment (Haas et al., 1994). Poor engraftment places the patient at increased risk for infections, bleeding, or death. Additionally, an increased need for transfusions is likely (Schiller et al., 1995).

Patients who do not mobilize a sufficient number of HSCs need different mobilization strategies, multiple apheresis collections, or possibly a bone marrow harvest. Different remobilization strategies that have been used include an increased dose of G-CSF or GM-CSF, mobilization with cytokines and chemotherapy, or possible inclusion in clinical studies (Schmit-Pokorny, 2004; Stiff, 1999). These remobilization strategies add additional cost, the potential for more toxicity, and increased product volume, which may lead to increased toxicities when the graft is infused.

### Novel Agents for Mobilization

Novel strategies for patients who do not collect sufficient numbers of HSCs with current mobilization strategies are needed. Other cytokines for mobilization have been investigated, including interleukin-3 (Vose et al., 1992); PIXY321, a fusion product of GM-CSF and interleukin-3 (Bishop et al., 1996); recombinant human stem cell factor (Glasy et al., 1997); recombinant human erythropoietin, also known as epoetin alfa (Kessinger & Sharp, 1996); and pegfilgrastim (Staber, Holub, Linkesch, Schmidt, & Neumeister, 2005). The results of these clinical trials produced results similar to the results with G-CSF or GM-CSF for mobilization.

Plerixafor initially was developed as an inhibitor of HIV entry into T cells. However, during clinical trials in HIV-positive patients and healthy volunteers, leukocytosis was observed, prompting an investigation into why this occurred and what cells were affected (Hendrix et al., 2004; Liles et al., 2005). It was discovered that the leukocytes were CD34+ cells and plerixafor's ability to act as an HSC mobilizer was identified (Burger & Peled, 2009). Plerixafor was further explored as a mobilizing agent for HSCT. Preclinical and clinical trials demonstrated that plerixafor alone and in combination with G-CSF mobilizes HSCs (Broxmeyer et al., 2005; Devine et al., 2004; Liles et al., 2003). Plerixafor, a chemokine antagonist, is a reversible inhibitor of SDF-1α/CXCR4 binding and has been shown to efficiently mobilize HSCs into the peripheral circulation.

In a phase II study, patients with multiple myeloma (MM) or non-Hodgkin lymphoma (NHL) were randomized to a crossover study in which they received either plerixafor with G-CSF then G-CSF alone or G-CSF alone followed by plerixafor with G-CSF (Flomenberg et al., 2005). In 84% of patients, the combination of plerixafor and G-CSF was found to mobilize 50% or more HSCs compared to G-CSF alone. The most common side effects attributed to plerixafor were gastrointestinal symptoms (e.g., upset stomach, flatulence), injection site erythema, and paresthesias. The authors found that the increase in CD34+ cells was higher in patients with NHL than in patients with MM. In this study, plerixafor was administered at 8 am followed by apheresis six hours later. This may present some scheduling or logistical issues. The patients in the study engrafted in a median of 10 days, which is comparable to other mobilization regimens.

In a compassionate use study, plerixafor was used with G-CSF as an attempt to mobilize patients who failed previous attempts...
were similar across the treatment groups (10–11 days and 18–20 days, respectively). The most common adverse events attributed to plerixafor use were gastrointestinal disorders (e.g., diarrhea, nausea, vomiting) and injection site reactions. The authors concluded that plerixafor was well tolerated and allowed patients to collect the optimal target CD34+ cells/kg with fewer apheresis procedures compared to using G-CSF alone (DiPersio, Micallef, et al., 2009; DiPersio, Stadmauer, et al., 2009). A summary of plerixafor side effects and nursing implications is shown in Tables 4 and 5 as a summary of the side effects and nursing implications of G-CSF.

In December 2008, plerixafor was approved by the FDA for use in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with NHL and MM.

### Apheresis Process, Goals, and Care

Apheresis is the processing of whole blood into its separate components so that one particular component can be collected and stored. The criteria to begin apheresis for the collection of HSCs vary based on the standards of individual transplantation centers. Criteria used by transplantation centers include the total white blood cell count, the absolute neutrophil count, the number of circulating CD34+ cells, or the number of days of

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**Table 3. Mobilization Regimens and Corresponding CD34 Cell Yields**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DISEASE STATE</th>
<th>MOBILIZATION REGIMEN</th>
<th>N</th>
<th>MEDIAN TOTAL COLLECTED CD34 CELLS X 10⁶/KG (RANGE)</th>
<th>MEDIAN APERHESIS SESSIONS (RANGE)</th>
<th>NUMBER OF MOBILIZATION FAILURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alegre et al., 1997</td>
<td>MM</td>
<td>G-CSF</td>
<td>22</td>
<td>4.85 (2.1–10.05)</td>
<td>3 (2–6)</td>
<td>NR</td>
</tr>
<tr>
<td>Bensinger et al., 1997</td>
<td>MM, L, BC, O</td>
<td>Chemotherapy + G-CSF or GM-CSF</td>
<td>124</td>
<td>10.75 (0.01–178.33)</td>
<td>3 (1–9)</td>
<td>9</td>
</tr>
<tr>
<td>Dazi et al., 2000</td>
<td>NHL</td>
<td>G-CSF</td>
<td>12</td>
<td>2.89 (1.7–5.6)</td>
<td>16 total⁶</td>
<td>NR</td>
</tr>
<tr>
<td>Desikan et al., 1998</td>
<td>MM</td>
<td>G-CSF</td>
<td>22</td>
<td>5.8 (NR)</td>
<td>5</td>
<td>23%⁶</td>
</tr>
<tr>
<td>Narayanasami et al., 2001</td>
<td>NHL, HD</td>
<td>G-CSF</td>
<td>22</td>
<td>2.5 (0.3–12.4)</td>
<td>NR (1–3)</td>
<td>1</td>
</tr>
<tr>
<td>Pavone et al., 2002</td>
<td>NHL</td>
<td>DHAP = G-CSF</td>
<td>38</td>
<td>5.9 (NR)</td>
<td>2 (1–3)</td>
<td>5</td>
</tr>
<tr>
<td>Pusic et al., 2008</td>
<td>NHL, HD, MM</td>
<td>G-CSF</td>
<td>976</td>
<td>3.34 (NR)</td>
<td>2 (1–5)</td>
<td>182</td>
</tr>
</tbody>
</table>

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⁶Reports included in this table were randomized, controlled trials and other studies involving 24 or more patients with MM or NHL that reported CD34 cell yields stratified according to mobilization regimen.

⁷Total number of apheresis sessions for all patients in the group

¹Percentage is reported instead of n value.

⁸Mean value is reported instead of median.

**BC**—breast cancer; **CD**—cluster of designation; **CY**—cyclophosphamide; **DHAP**—etoposide, cytosine arabinoside, methylprednisolone, and cisplatin; **G-CSF**—granulocyte–colony-stimulating factor; **GM-CSF**—granulocyte macrophage–colony-stimulating factor; **HD**—Hodgkin disease; **L**—lymphoma; **MM**—multiple myeloma; **NHL**—non-Hodgkin lymphoma; **NR**—not reported; **O**—other

Apheresis consists of removing whole blood from the circulation and separating the blood into individual components: red blood cells, plasma, white blood cells, and platelets based on the component’s density. Red blood cells are the most dense, and the plasma and platelets are the least dense. HSCs circulate in the buffy coat layer, which lies between the layer of red and white blood cells. The buffy coat layer, including the HSCs, flows into a collection bag; the other blood components are returned to the patient.

Multiple apheresis procedures may be required for a patient to meet the target collection goal. Typically, the quantity of blood processed in a single apheresis session is three to four times the total blood volume and takes four to six hours. The length of time is determined by patient size, total blood volume, blood flow rate, and patient tolerance. The higher the number of circulating CD34+ cells correlates with a higher number of CD34+ cells collected and fewer apheresis procedures (Bensinger et al., 2009).

An anticoagulant is added to the blood during processing to prevent clotting of lines and clumping of the product. The most common anticoagulant is citrate dextrose, which can decrease the serum level of ionized calcium, causing symptoms of hypocalcemia, outlined in Table 6. In a retrospective study of 540 collections, paresthesias from citrate toxicity was the most prevalent adverse event (20%) during collection (Moog, 2001). Untreated low serum calcium may progress to nausea, vomiting, loss of consciousness, tetany, and seizures (Rowley, 2000). Low calcium can be prevented or minimized by the administration of oral calcium supplements, IV calcium gluconate, and decreasing the blood flow rate during collection.

Central catheter-related issues with positioning or clotted veins can interrupt or slow the collection process. Moog (2001) described central catheter-related issues in 7% of patients that included blood flow alarms (11%) and blockages in the return line (4%). Other side effects of apheresis (e.g., lightheadedness, dizziness, chills, fever, urticaria, hypotension) are generally mild and transient. Antihypertensive medications can worsen hypotension and should be held prior to apheresis. The hematocrit and platelet count can be temporarily lowered because of apheresis, and each transplantation center has guidelines for red blood cell or platelet transfusion. Table 6 summarizes potential complications of apheresis.

Although most patients tolerate apheresis without significant incident, all patients should undergo a thorough physical examination and medical history prior to beginning apheresis.

Table 4. Common Side Effects of Plerixafor and Nursing Interventions

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>ASSESSMENT</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diarrhea and abdominal distention</td>
<td>Monitor number of episodes.</td>
<td>Instruct patient that diarrhea may occur as early as 1–1.5 hours after administration. Patients should have anti-diarrheal medications readily available to use at home. Antiemetics</td>
</tr>
<tr>
<td>• Nausea</td>
<td>Monitor fluids.</td>
<td></td>
</tr>
<tr>
<td>Skin reactions at injection site</td>
<td>Monitor sites.</td>
<td>Notify physician for evaluation if not resolving or causing discomfort to patient.</td>
</tr>
<tr>
<td>Headache or flu-like symptoms</td>
<td>Monitor frequency and intensity.</td>
<td>Administer analgesics. Notify physician for persistent or severe complaints.</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Baseline pulse, blood pressure Monitor after injection.</td>
<td>Administer or instruct patient to administer while sitting. The patient should wait 5–10 minutes before rising and should rise slowly.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Monitor platelet counts.</td>
<td>Notify physician if less than 50,000 mm³. Monitor for post-procedure bleeding. Administer platelet products. Educate patient about thrombocytopenic precaution if less than 50,000 mm³.</td>
</tr>
</tbody>
</table>

*Note.* Based on information from Calandra et al., 2008; Flomenberg et al., 2005; Genzyme Corporation, 2008.

Cytokine administration. Based on its ability to process large volumes, a continuous-flow apheresis device which simultaneously collects, spins, and returns blood often is used in the collection of HSCs. Some patients have adequate antecubital veins to support a vein-to-vein procedure; however, if they do not, a large-bore dual-lumen venous access catheter may be surgically inserted. Patients who have received previous chemotherapy and are proceeding to autologous HSCT may have the central line placed prior to mobilization so that it can be used for collection of HSCs and for the HSCT.

Table 5. Common Side Effects of Filgrastim and Nursing Interventions

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>ASSESSMENT</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>Monitor frequency and intensity.</td>
<td>Educate patient that bone pain can be expected. Administer analgesics. Notify physician of persistent or severe complaints.</td>
</tr>
<tr>
<td>• Nausea or anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diarrhea or constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin reactions or bruising at injection site</td>
<td>Monitor sites.</td>
<td>Notify physician for evaluation if not resolving or causing discomfort to patient.</td>
</tr>
<tr>
<td>Headache or flu-like symptoms</td>
<td>Monitor frequency and intensity.</td>
<td>Administer analgesics. Notify physician of persistent or severe complaints.</td>
</tr>
<tr>
<td>Liver function test (LFT)</td>
<td>Monitor LFT, transient increases in alkaline phosphatase, and lactate acid dehydrogenase.</td>
<td>Instruct patient that transient increases may occur. Monitor laboratory results for normalization after filgrastim therapy is discontinued.</td>
</tr>
</tbody>
</table>

*Note.* Based on information from Amgen Inc., 2007; Schmit-Pokorny, 2004.
The apheresis session requires a nurse adept at troubleshooting issues with the central or peripheral access as well as the apheresis device. Patients require close monitoring throughout the apheresis procedure to ensure their safety and comfort.

### Cell Processing

Once the HSCs are collected, the product is taken to the laboratory for processing and cryopreservation. The processing of the autologous graft includes sterility testing, blood typing, and a reduction in fluid volume (Schmit-Pokorny, 2004). Understanding the science of HSC cryopreservation is beyond the scope of this article, but a review of the basic principles will complement nurses’ overall knowledge of transplantation and explain some of the side effects that nurses may observe during the infusion of the graft.

Rowley (2004) outlined six principles of HSC cryopreservation. The first principle is to reduce the number of mature blood cells in the graft because mature blood cells do not tolerate cryopreservation well. The second principle is to protect the cells from ice formation and dehydration during freezing. A cryoprotectant, such as dimethylsulfoxide or hydroxyethyl starch, can be used to accomplish this goal. Reducing the risk of cell injury during cryopreservation is the third principle and can be accomplished by adding plasma protein to the graft. Saline or tissue culture media can be used to provide suspension of the cells and serve as a diluent for the cryoprotectants to meet the fourth principle of cryopreservation. The fifth principle is controlled cooling of the hematopoietic cell graft. The rate of freezing for hematopoietic cells when using the cryoprotectant dimethylsulfoxide is 1°C–3°C per minute. The sixth principle is related to the storage of the cells. Cells must be stored at a temperature that protects the cells from ice recrystallization and cell damage. HSCs should be stored at temperatures below −120°C in liquid nitrogen or mechanical freezers.

Reducing the volume of the hematopoietic cell graft leads to a reduction in the amount of cryoprotectant that is needed during freezing. This has a direct impact on the care of the patient during the infusion of the autologous graft (Schmit-Pokorny, 2004). Most of the side effects observed during infusion of the cells from ice formation and dehydration during freezing. A cryoprotectant, such as dimethylsulfoxide or hydroxyethyl starch, can be used to accomplish this goal. Reducing the risk of cell injury during cryopreservation is the third principle and can be accomplished by adding plasma protein to the graft. Saline or tissue culture media can be used to provide suspension of the cells and serve as a diluent for the cryoprotectants to meet the fourth principle of cryopreservation. The fifth principle is controlled cooling of the hematopoietic cell graft. The rate of freezing for hematopoietic cells when using the cryoprotectant dimethylsulfoxide is 1°C–3°C per minute. The sixth principle is related to the storage of the cells. Cells must be stored at a temperature that protects the cells from ice recrystallization and cell damage. HSCs should be stored at temperatures below −120°C in liquid nitrogen or mechanical freezers.

### Table 6. Potential Complication of Apheresis

<table>
<thead>
<tr>
<th>POTENTIAL COMPLICATION</th>
<th>ETIOLOGY</th>
<th>ASSESSMENT</th>
<th>NURSING INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia</td>
<td>Sodium citrate used to prevent blood from clotting in the apheresis machine binds ionized calcium.</td>
<td>Baseline serum calcium Monitor ionized calcium.a</td>
<td>Notify physician if low Slow flow rate and offer oral calcium, liquid, or tablets Increase calcium-containing foods Oral calcium supplements IV calcium gluconate</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Extracorporeal volume greater than patient tolerance</td>
<td>Baseline pulse, blood pressure, Hgb/Hct, and health history Brief physical assessment and vital signs every five minutes initially, gradually decreasing frequency as patient’s tolerance is established Assess for hypotension, tachycardia, light-headedness, diaphoresis, and dysrhythmias.</td>
<td>Notify physician of abnormal or unexpected findings before proceeding Interrupt the procedure until the patient is stable, then resume at a slower flow rate and minimal extracorporeal volume. Monitor physical status and vital signs closely. Notify physician if symptoms persist or progress Administer blood products Administer fluid Hold angiotensin-converting enzyme inhibitor medication.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Collection of platelets into product</td>
<td>Baseline platelet count Ascertain whether platelet-rich plasma will be returned at the procedure’s completion.</td>
<td>Notify physician if less than 50,000 mm³ Monitor for signs of post-procedure bleeding Administer platelet products.</td>
</tr>
<tr>
<td>Issues related to the catheter</td>
<td>Positional or clotted catheter</td>
<td>Pressure alarms from apheresis machine identifying access or return-line issues</td>
<td>Troubleshoot access lines and apheresis machine Reposition patient.</td>
</tr>
<tr>
<td>Miscellaneous effects</td>
<td>• Chilling</td>
<td>Cooling of blood while circulating in the apheresis machine Previous chemotherapy regimens Pediatric patients with less developed hematopoietic progenitor pool</td>
<td>Observe for chilling.</td>
</tr>
<tr>
<td></td>
<td>• Prolonged cytopenia</td>
<td></td>
<td>Observe for headache. Observe daily CBC, Plt, and Diff.</td>
</tr>
</tbody>
</table>

*a Applies to pediatric patients

CBC—complete blood count; Diff—differential; Hct—hematocrit; Hgb—hemoglobin; Plt—platelets

*Note. Based on information from Hooper & Santos, 1993; Schmit-Pokorny, 2004.*
Nursing Implications

Improving the quality of life for patients during the mobilization process is an important nursing goal. Mobilization strategies are unpredictable because of the variability of white blood cell recovery and the number of collection days required to meet the collection goal. Medical complications are possible, including the risk of infection during the neutropenic period following chemotherapy mobilization. A large number of collections and medical complications add to a patient’s out-of-pocket expenses and lifestyle disruptions. Patients may benefit from novel mobilization strategies. Future research regarding the quality of life throughout the mobilization and collection phase of HSCT may validate these issues. From an administrative perspective, many economic opportunities should be explored that include the overall time and complexity of the coordination of mobilization and HSC collection orders; communicating with clinical staff, apheresis department, stem cell laboratory, the inpatient and outpatient treatment areas; and costs associated with cryopreservation storage. Understanding risk factors associated with patients who may be difficult to mobilize, developing mobilization treatment algorithms, and incorporating the use of novel agents may improve the predictability of HSC numbers, timing, collection, and center efficiency. A cost analysis of current strategies throughout the mobilization phase of HSCT may validate the cost savings of using the most efficient method in HSC procurement.

Conclusion

As the knowledge of stem cell biology increases, new strategies will be developed to improve mobilization of HSCs for autologous HSCT. Nurses working in the field of HSCT need to understand stem cell biology and the mechanisms of action of current mobilization strategies. Historical methods of stem cell mobilization include cytokines alone or in combination with chemotherapy. Plerixafor, a chemokine antagonist approved by the FDA for use in combination with cytokines, may ultimately change how HSCs are mobilized for autologous HSCT. Data demonstrate that chemokine antagonists can increase the number of HSCs collected, decrease the number of apheresis procedures, and improve the likelihood that more patients will proceed to a potentially curative autologous HSCT.

The authors take full responsibility for the content of the article. Devine, Tierney, Schmit-Pokorny, and McDermott are consultants for Genzyme Corporation. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff.

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References


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