Article

Clinical Updates in Blood and Marrow Transplantation in Multiple Myeloma

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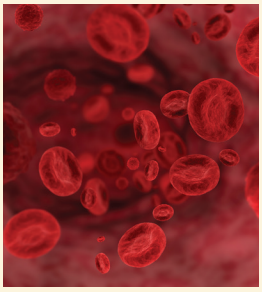

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The process of hematopoietic stem cell transplantation (HSCT) is well defined, yet debate remains surrounding the role and timing of HSCT in patients with multiple myeloma (MM). Since the 1980s, survival advances have been made with the use of newer agents by recognizing the role of transplantation, identifying the anticipated side effects at each phase, and improving supportive care strategies. Data support transplantation as part of the treatment strategy, but the optimal induction regimen and timing of transplantation have yet to be defined. The general consensus is that eligible patients should undergo autologous HSCT at some point in the treatment spectrum, preferably earlier rather than later in the disease. Allogeneic transplantation is only recommended in the context of a clinical trial and in patients with high-risk disease. The transplantation process can be overwhelming for patients and caregivers. Nurses play a key role in improving outcomes by caring for patients and families throughout the transplantation experience and, therefore, need to be knowledgeable about the process. This article is intended to expand discussion on the role of nurses in assisting patients and families undergoing transplantation to include an overview of the acute care phase of the transplantation process.

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The process of transplantation can be conceptualized through several phases (see Figure 1). Each phase carries with it distinct considerations and management strategies to optimize the overall process. Years of clinical research and experience have provided knowledge of when challenges, side effects, and appropriate interventions can occur. Thus, an experienced transplantation team can anticipate patient needs during the acute phase. Long-term side effects and complications can occur and require the attention of community-based practitioners, as well. This article will cover considerations within each phase, with a focus on autologous hematopoietic stem cell transplantation (AHSCT) and should be used in conjunction with the Miceli et al. (2013) article in this supplement to get a broad picture of the transplantation experience. Allogeneic transplantation, which should only be considered in the context of a clinical trial, is highlighted in the "Special Interest" sidebar on page 35.

Phase 0: Induction or Initial Treatment

Following a confirmed diagnosis of symptomatic multiple myeloma (MM), the patient begins induction chemotherapy. The goals of induction therapy are to induce a tumor response and decrease symptoms by reducing disease burden (Giralt, 2012). Response to therapy is classified based on the reduction of myeloma protein from baseline. A complete response is the best surrogate marker for progression-free survival (Chanan-Khan & Giralt, 2010). A complete response occurs when patients achieve negative immunofixation of the serum and urine, experience the disappearance of any soft tissue plasmacytomas, and

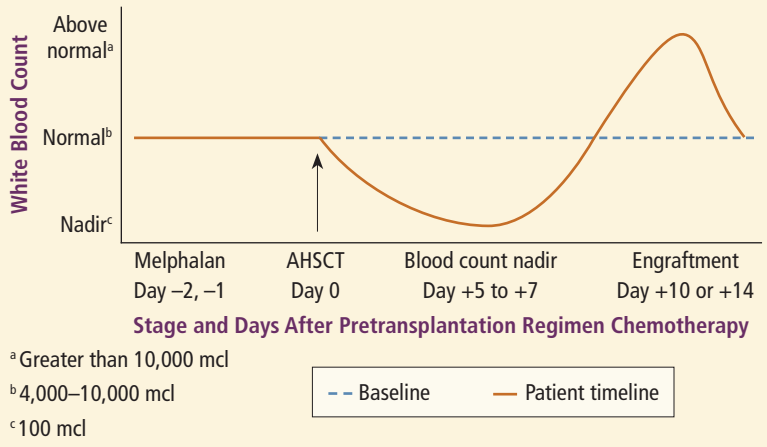

FIGURE 1. Timeline Schema for the Conditioning Regimen for Autologous Hematopoietic Stem Cell Transplantation (AHSCT)

Note. Based on information from Antin & Yolin Raley, 2009; Rodriguez, 2010.

reduce the number of plasma cells present in the bone marrow to 5% or less (Durie et al., 2006). Improved response rates can be seen with the newer therapies, such as lenalidomide, bortezomib, and carfilzomib, followed by AHSCT (Jakubowiak et al., 2012; Richardson et al., 2010; Rosiñol et al., 2012).

To date, the optimal timing of transplantation cannot be defined. Considerations include patient performance status, organ function, response to therapy, financial limitations, and the overall treatment plan. Participation in a well-designed clinical trial also should be considered to help identify the best induction therapy, transplantation timing, and maintenance therapy for each MM subgroup. When considering transplantation as part of the treatment plan, using stem cell–sparing induction regimens, which are less damaging to the hematopoietic stem cells (HSCs), is important. Some antimyeloma therapies (e.g., alkylating agents) can damage stem cells and negatively impact the ability to collect adequate amounts of peripheral blood HSCs for transplantation. In particular, the prolonged use of melphalan should be avoided in patients eligible for transplantation (Cavo et al., 2011; Giralt et al., 2009). Possible pretransplantation combinations for induction therapy are outlined in Miceli et al. (2013) and will not be discussed here.

Phase 1: Collection Process

A key component of the transplantation process is the acquisition of pluripotent HSCs. The sources of HSCs for transplantation are autologous (self-donation), syngeneic (identical sibling), and allogeneic (related or unrelated donation). As mentioned earlier, HSCs can be retrieved from the bone marrow, cord blood, or peripheral blood (Antin & Yolin Raley, 2009). Peripheral blood has become the most-used source for HSC collection (Pasquini & Wang, 2011). CD34+ cells are progenitor cells with the capacity to differentiate and repopulate myeloid and lymphoid cell lines following bone marrow ablation after high-dose chemotherapy. They are measured in cells per deciliter (cells/dl) to the power of 10^6 (million) based on recipient weight (i.e., collection yield of 3.2 x 10^6 CD34+ cells/kg recipient weight) (DisPersio, Stadtmauer, et al., 2009). Use of CD34+ cells has resulted in reduced transfusion needs and a shorter engraftment period following transplantation. Therefore, this has become the preferred source of progenitor cells (versus bone marrow) (Williams, Zimmerman, Grad, & Mick, 1993) and will be discussed in the current article.

Mobilization

The process of stimulating the bone marrow to release HSCs into the peripheral blood is called mobilization. Methods to mobilize HSCs from the bone marrow into the peripheral blood include the use of cytokine growth factors, such as granulocyte–colony-stimulating factor (G-CSF) (e.g., filgrastim), alone or in combination with chemotherapy or the CXCR4-binding agent plerixafor. For some patients, the use of G-CSF alone may mobilize adequate HSCs (Giralt et al., 2009). The approach may be effective for patients younger than 65 years who have not received melphalan or prolonged use of lenalidomide (Giralt et al., 2009). Key side effects of cytokine growth factors include leukocytosis, bone pain, myalgias, and flu-like symptoms. In addition, some patients may develop a low-grade fever (Amgen Inc., 2013).

For others, chemotherapy may be added to assist with the mobilization process and used as an additional treatment option prior to transplantation, particularly if optimal response has not been achieved. Although several different chemotherapies are eligible for use during the HSC mobilization process, including etoposide and paclitaxel, cyclophosphamide is used most frequently (Giralt et al., 2009). Common side effects related to high doses of cyclophosphamide include nausea, alopecia, and myelosuppression. At the doses used for mobilization, patients rarely will experience mucositis or hemorrhagic cystitis. However, patients are encouraged to drink plenty of fluids to reduce the risk of bladder toxicity (Rodriguez, 2010). They also must report to the nurse or provider a fever greater than 38.3°C (101°F) or a persistent fever of 38°C (100.4°F) when at blood count nadir (white blood count less than 100 mcl) (Palumbo et al., 2012). Nadir from cyclophosphamide, when used in combination with G-CSF for the purpose of HSC mobilization, is predictable and typically of short duration (8–12 days) (Giralt et al., 2009).

The newest approach to stem cell mobilization is the use of plerixafor with G-CSF. Plerixafor is a bicyclam molecule that binds to the CXCR4 receptor site, the stem cell honing site in the bone marrow stroma. Plerixafor temporarily blocks the SDF-1a signaling pathway necessary to bind CD34+ cells to the bone marrow, promoting circulation of the CD34+ cells into the peripheral blood. Plerixafor in combination with G-CSF was approved by the U.S. Food and Drug Administration in December 2008 for stem cell mobilization in autologous donors with non-Hodgkin lymphoma and MM (DiPersio, Uy, Yasothan, & Kirkpatrick, 2009; Flomenberg et al., 2005; National Cancer Institute, 2013). Side effects associated with plerixafor include leukocytosis, thrombocytopenia, diarrhea, nausea, erythema at the injection site, and fatigue (Genzyme Corporation, 2010).

The combination of plerixafor and G-CSF has been shown to be more effective at mobilizing HSCs than G-CSF alone (DiPersio, Stadtmauer, et al., 2009). Using G-CSF in conjunction with

plerixafor results in higher success rates for mobilizing more stem cells while undergoing fewer apheresis procedures. As a result, more patients achieve the minimum and target amounts of stem cells needed for transplantation. Use of plerixafor also has significantly reduced the number of mobilization failures. Even patients who previously failed to effectively mobilize HSCs have been successful with the use of plerixafor, allowing more patients to proceed to transplantation (Calandra et al., 2008; Gopal et al., 2012).

The cost of two common HSC mobilization approaches has been compared in the literature (Gertz, Wolf, Micallef, & Gastineau, 2010; Micallef et al., 2013). Investigators at Memorial Sloan-Kettering Cancer Center in New York, NY, and the Mayo Clinic in Rochester, MN, performed a retrospective analysis of all patients with MM treated from November 2008 to March 2011 who received cyclophosphamide plus G-CSF or plerixafor plus G-CSF as the first-line mobilization regimen. Plerixafor was more cost effective than the more widely used cyclophosphamide. Plerixafor plus G-CSF costs less than cyclophosphamide plus G-CSF because plerixafor requires fewer days of apheresis (Adel et al., 2011). Another reason for lower cost is that patients who use plerixafor are less likely to require hospitalization because of infections. Despite the cost of the medication, the notable benefits for successful mobilization make it a cost-effective option, particularly for patients at risk for mobilization failure (Gertz et al., 2010; Micallef et al., 2013).

The combined mobilization regimen of G-CSF and plerixafor should begin four days prior to planned harvest. G-CSF is given at a dose of 10 mcg/kg daily, by subcutaneous injection, beginning on day –4. The recommended dose of plerixafor is 0.24 mg/kg given by subcutaneous injection about 11 hours prior to each planned apheresis session, beginning on day –1. The dose of plerixafor should not exceed 40 mg per day, and should be adjusted for creatinine clearance less than 50 ml per minute (Genzyme Corporation, 2010). One study suggested that the administration of plerixafor 17 hours prior to collection, rather than 11 hours, was as effective and more convenient for patients and nurses (Harvey et al., 2011).

Collection

The goal of collection is to procure a sufficient number of HSCs for reconstitution of hematopoietic function after high-dose chemotherapy (HDC) is administered to eradicate the MM. Cells are collected via apheresis using a large bore catheter in a process that separates blood components and selects specific cells for use. Although the ideal stem cell collection goal is greater than 3 x 10^6 CD34+ cells/kg of recipient weight, 2 x 10^6 CD34+ cells/kg of recipient weight offers a minimum goal when HSC yield is low. Greater cell counts allow for faster recovery of hematopoiesis. Some patients may want to store additional cells for a future transplantation (Gertz et al., 2010; Giralt et al., 2009).

Once collected, the cells are cryopreserved in a medium of dimethyl sulfoxide (DMSO) to prevent cell breakdown, and may be stored for an indefinite period of time (Antin & Yolin Raley, 2009; Gertz et al., 2010). Stem cell collection can occur days, months, or even years prior to HDC, but typically occurs early in the diagnosis to ensure adequate collections before patients are exposed to extended chemotherapy (Antin & Yolin Raley, 2009; Gertz et al., 2010).

Phase 2: Pre-Engraftment

The decision to proceed directly to HDC and AHSCT is individualized based on many patient-specific factors (see Figure 2). It may follow the mobilization and collection phase for early transplantation, or may be postponed until a later date at

Special Interest: HSCT, Allogeneic HSCT, and Acute GVHD

Allogeneic HSCT uses HDC similar to autologous HSCT, but instead uses HSCs from a donor. The donor cells are used to reconstitute the bone marrow function after HDC while producing a new immune system in the recipient. The new immune function can provide a graft-versus-tumor benefit, but is associated with high treatment-related mortality from intensive conditioning regimens, infection associated with immunosuppression, and GVHD.

Acute GVHD is a major complication of allogeneic HSCT associated with significant morbidity and mortality. GVHD occurs when donor-derived cells recognize recipient tissue as foreign and mount an immune attack against the patient's own tissues, which occurs in 40%–60% of patients undergoing allogeneic HSCT. Although GVHD is a complication of transplantation, it also is considered a treatment for multiple myeloma. As GVHD occurs, graft-versus-myeloma causes an antitumor effect mediated by the donor graft.

Clinical manifestations of acute GVHD can be seen in the immune system, skin, gut, and liver. Transplantation recipients with acute GVHD may present with rash (81%), gut (54%), and liver (50%) symptoms. Acute GVHD has a significant impact on the immune system. Immune reconstitution is an integral part in the prevention of opportunistic infections, and infection is the most frequent cause of death in transplantation recipients who experience acute GVHD. Not only does prolonged myelosuppression occur in these patients, thymic involution and hypogammaglobulinemia further weaken the immune system.

A skin rash often is the initial symptom associated with acute GVHD. The rash typically is described as maculopapular, and often begins in the anterior or posterior torso, neck, palmar and plantar surfaces, and ears. The typical rash can range from a sunburn-like appearance to desquamating and peeling skin.

The symptoms of gastrointestinal acute GVHD include nausea, emesis, diarrhea, abdominal cramping, and pain. Hematochezia, ileus, and anorexia are other notable side effects associated with acute GVHD.

Liver acute GVHD is caused by damage to the bile canaliculi, which can cause cholestasis with hyperbilirubinemia and elevated alkaline phosphatase. The severity of liver acute GVHD is based on the serum bilirubin.

Ruling out other causes of organ dysfunction, such as drug toxicity (skin, gut, liver), viral infection (gut, liver), and sinusoidal obstructive syndrome (liver) is important. Prevention of acute GVHD begins with donor selection and continues with immunosuppressive medication to decrease T-cell activation and proliferation.

Common medications used in the prevention and treatment of GVHD include cyclosporine, methotrexate, mycophenolate mofetil, steroids, sirolimus, and tacrolimus. In addition, bortezomib is an experimental medication for this use.

GVHD—graft-versus-host disease; HDC—high-dose chemotherapy; HSCT—hematopoietic stem cell transplantation

Note. Based on information from Antin & Yolin Raley, 2009; El-Cheikh et al., 2013; Koreth et al., 2012; Laffan & Biedrzycki, 2006; Lokhorst et al., 2010; Martin et al., 1990; Mattson, 2007; Pallera & Schwartzberg, 2004; Sung & Chao, 2013.

the time of relapse (Kumar, 2009). If chemotherapy is used for stem cell mobilization, some centers may delay HDC to allow recovery and avoid the added risk of marrow toxicity.

The amount of time to undergo Phase 2 (pre-engraftment) typically is measured in weeks. The process includes three components: conditioning, stem cell infusion, and supportive therapy through engraftment (Antin & Yolin Raley, 2009). During this time, the recipient may be an inpatient at the transplantation center for three to four weeks, requiring geographic relocation if the transplantation center is not near the patient's home. Some centers perform the AHSCT process in the outpatient department, which requires a trained caregiver (Kurtin, Lilleby, & Spong, 2013) and daily clinic visits to monitor side effects.

Conditioning

The therapy used prior to HSCT is referred to as *conditioning*. The term refers to the process of getting the bone marrow in condition to receive new cells. In patients with MM, high-dose melphalan (HDM) is the chemotherapy agent of choice (Bensinger, 2009). Total body irradiation is no longer routinely used as part of the conditioning regimen because of increased toxicity without survival benefit (Moreau et al., 2002). The standard dose of high-dose melphalan is 200 mg/m^2 via infusion. Dose reductions are made if patients have impaired renal function, advanced age, or comorbid conditions. A 24-hour rest period often is planned after high-dose melphalan and before HSC infusion to avoid the risk of cytotoxicity on newly infused HSC (Talamo et al., 2012).

Age
- Chronologic age does not eliminate transplantation as a treatment option; consider physiologic age for determining eligibility.

Cardiac
- Left ventricular ejection fraction (LVEF) greater than 50%
- If LVEF is less than 50% or history of heart failure exists, evaluation and intervention to optimize heart function are recommended.

Disease
- High risk versus standard risk
- Responding to therapy or progressing on therapy

Performance Status
- Karnofsky Performance Score (KPS) or Eastern Cooperative Oncology Group (ECOG) provide guidance of performance status; generally, KPS greater than 60% or ECOG performance status greater than 3 is needed to proceed to transplantation.

Pulmonary
- Adequate lung function (diffusion capacity of the lung for carbon monoxide) greater than 50%
- Discontinuation of tobacco products
- Treat underlying pulmonary process, including infection.

Renal Insufficiency or Failure
- If on dialysis or if creatinine clearance is less than 50 ml per minute, medications will be renal-dose adjusted; dialysis does not preclude transplantation as a treatment option.

Socioeconomic Factors
- Financial: Insurance coverage (e.g., private, Medicaid, Medicare)
- Social: Caregiver support during and following transplantation
- Personal philosophy: Does the patient want to undergo transplantation? Are they accepting of transfusion support?

FIGURE 2. Factors to Consider When Determining Eligibility for Transplantation

Note. Based on information from Antin & Yolin Raley, 2009; Palumbo et al., 2012.

Stem Cell Infusion

At this stage of the process, the previously cryopreserved HSCs are systematically thawed and infused into the patient via a central venous catheter. The day of infusion is commonly referred to as "Day 0." The actual infusion can take an hour or longer, depending on the number of frozen bags of stem cell product to administer. The patient will have a distinctive odor after the infusion because of the DMSO preservative, which is most noticeable with respiration and voiding. The odor has been described as similar to creamed corn or garlic, and gradually diminishes in two or three days. Patients also can taste the DMSO. Various studies have been conducted to attempt to decrease this unpleasant effect. Some patients have sucked on an orange or lemon during the infusion to decrease the taste of the DMSO (Potter, Eisenberg, Cain, & Berry, 2011). Other activities that are part of the infusion, such as hydration and frequent vital sign monitoring, will result in a day-long procedure (Antin & Yolin Raley, 2009).

Supportive Therapy

Although pretransplantation testing is designed to preclude patients with baseline renal, liver, cardiac, and pulmonary dysfunction from transplantation, end-organ complications may occur during the pre-engraftment phase of the transplantation process (Laffan & Biedrzycki, 2006; Pallera & Schwartzberg, 2004). HDM and AHSCT are associated with expected side effects such as alopecia, gastrointestinal (GI) toxicities, and bone marrow ablation. The side effects of HDM are not present at the time of chemotherapy infusion, but are delayed as rapidly dividing cells are damaged from the effects of HDC. Complications of end-organ toxicity and life-threatening side effects may cause mortality not related to relapsed disease (Sorror, 2010), such as infectious issues and pulmonary complications. Anticipated side effects and other pre-engraftment complications are discussed in the following sections. An overview of common side effects associated with MM therapies and post-transplantation symptoms also can be found in Tables 1 and 2 on pages 17 and 19 in Miceli et al. (2013).

Alopecia: Psychosocial support and counseling regarding hair loss is important for men and women (Hesketh et al., 2004). Use of a wig or head gear may be comforting as well as functional to provide safety and warmth. The expense of a wig may be covered by insurance if ordered as a hair prosthetic.

Gastrointestinal toxicities: GI toxicity may include mucositis, esophagitis, nausea, vomiting, and diarrhea. Antiemetic therapy, hydration, and pain medication often are needed for management (Antin & Yolin Raley, 2009; Rodriguez, 2010). Patients experiencing GI toxicities may develop weight loss, anorexia, dehydration, and infection (Pallera & Schwartzberg, 2004; Rodriguez, 2010). Mucositis is a common side effect of HDM. A study compared sucking on ice chips versus swishing saline prior to and for two hours following the melphalan infusion to reduce the severity and duration of mucositis by decreasing the circulation of the chemotherapy through the oral tissues. The findings were significant in that the incidence of grade 3–4 mucositis was only

TABLE 1. Potential Gastrointestinal Symptoms and Treatments

Toxicity	Etiology	Intervention
Abdominal pain	Bowel obstruction Infection Acute graft-versus-host disease Venocclusive disease (VOD) or sinusoidal obstructive syndrome (SOS)	Surgical assessment and interventions Appropriate antibiotics or antifungals Immunosuppressive therapy changes, as indicated Supportive care if VOD or SOS develops • No standard treatment exists; however, several antithrombotic agents such as heparin or defibrotide are used. • Other treatment strategies include prostaglandin, antithrombin III concentrate, activated protein C, and prednisone.
Acute graft-versus-host disease	Donor cells in allogeneic transplantation[a]	Prophylactic immunosuppression and consider modifying immunosuppressive therapy Supportive therapy Monitor for infection
Anorexia	Chemotherapy Acute graft-versus-host disease Infection	Often temporary in the pre-engraftment phase Supportive care with hydration, electrolyte replacement, and nutritional support Immunosuppressive therapy, as indicated Antibiotics, antifungals, or antiviral therapy
Diarrhea	Chemotherapy Infection Acute graft-versus-host disease Bowel obstruction	Supportive care consisting of electrolyte replacement and hydration Infections such as *Clostridium difficile* should be treated with the appropriate antibiotics. Immunosuppressive therapy
Glucose abnormalities	Increase in glucose needs caused by infection, steroids Decrease in glucose caused by anorexia, diarrhea, nausea, and vomiting	If increase in glucose, consider insulin replacement and treat cause. If hypoglycemia, treat cause and administer glucose as indicated.
Mucositis	Chemotherapy Infection	Pain medication as needed Supportive therapy consisting of hydration or electrolyte replacement
Nausea and vomiting	Chemotherapy Acute graft-versus-host disease Infection	Antiemetic therapy Immunosuppression prophylaxis ordered and modified as indicated Antibiotics, antifungals, or antiviral prophylaxis may be ordered and changed as indicated.

[a] Occurs less often with autologous stem cell transplantation

Note. Based on information from Miceli et al., 2013; Pallera & Schwartzberg, 2004; Tuncer et al., 2012.

14% in the ice chip group compared to 74% in the saline group (Lilleby et al., 2006). Although the results support the use of ice chips to decrease oral mucositis during melphalan infusion, not all centers currently use this practice.

GI toxicities can be multifactorial, and all aspects of the symptoms should be considered. For example, a transplantation recipient may report pain from oral mucositis. The intervention may consist of oral care and pain management. Medication used to control pain potentially could cause nausea and constipation, creating a clinical challenge for the nursing staff caring for the patient. The goal of supportive care is not only to alleviate symptoms, but also to prevent additional GI problems such as ileus, anorexia, and infection (Cooke, Grant, & Gemmill, 2012). Inability to maintain oral intake because of GI toxicity may require the patient to be admitted to the hospital for closer monitoring and medication administration. Supportive care guidelines vary with each transplantation center (see Table 1).

Myelosuppression: When bone marrow ablation occurs, patients experience profound pancytopenia for about 10–14 days. Anemia and thrombocytopenia are managed by transfusion support based on laboratory parameters and patient symptoms. Transplantation recipients receiving HDC will develop severe neutropenia and are at risk for infection and sepsis. Infection risk is based on the type of transplantation, source of hematopoietic cells, underlying disease, disease status, conditioning regimen, prior infections, and environmental exposure to micro-organisms (Bevans et al., 2009). Antibiotics for bacteria, viruses, and fungi are used prophylactically when the absolute neutrophil count is less than 500 cells/dl, as well as therapeutically for febrile neutropenia or occult infection (Subramanian, 2011). Common sources of infection include central line infections, GI infections such as *Clostridium difficile* (*C. diff*), and skin infections. However, enteric organisms (*Escherichia coli*) and opportunistic infections such as *Pneumocystis jiroveci* also are common during this time (Pallera & Schwartzberg, 2004). Figure 3 lists infectious organisms commonly seen in transplantation recipients during the pre-engraftment period. Many transplantation centers attempt to minimize infection by recommending a low-pathogen environment. Most centers use a Laminair flow filtration system to provide such an environment (Solomon et al., 2010).

Renal dysfunction: Renal failure can occur at any time throughout the spectrum of the AHSCT process. When renal problems occur before stem cell engraftment, the cause can be multifactorial.

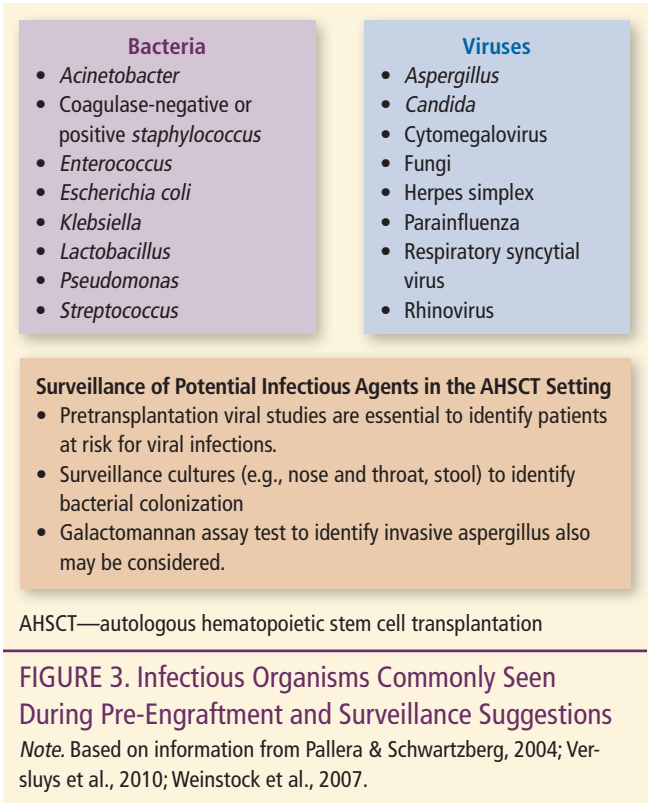

FIGURE 3. Infectious Organisms Commonly Seen During Pre-Engraftment and Surveillance Suggestions

Note. Based on information from Pallera & Schwartzberg, 2004; Versluys et al., 2010; Weinstock et al., 2007.

The source of the problem often is linked to nephrotoxic medication such as antibiotics, antihypertensives, chemotherapy, or antifungal agents. Acute renal failure from tubular necrosis may develop. Dehydration from diarrhea, nausea and vomiting, or anorexia also could cause impaired renal function. Other causes of renal problems in the early phase of transplantation include sepsis or relapsed MM (Pallera & Schwartzberg, 2004).

Pulmonary complications: Pulmonary complications are estimated to occur in 30%–60% of hematopoietic transplantation recipients. Certain chemotherapy agents can cause pulmonary complications in the early phase of transplantation. Pre-engraftment pulmonary complications include pulmonary edema, bronchiolitis obliterans, and pneumonia (Blombery et al., 2011). Common organisms causing pneumonia are listed in Table 3 of Miceli et al. (2013) on page 20 of this supplement.

Diffuse alveolar hemorrhage (DAH) is characterized by multilobular culture-negative lung injury. An estimated 5% of all HSCT recipients develop DAH, with an estimated mortality rate of 30%–60%. Presenting symptoms include acute shortness of breath, hemoptysis, fever, chest pain, and cough. Risk factors include older age, total body irradiation, severe mucositis, renal insufficiency, and white blood cell recovery. The definitive diagnosis of DAH is made by identifying bloody return on bronchoalveolar lavage. Early diagnosis is imperative, and treatment consists of corticosteroids and supportive care (Lara & Schwartz, 2010; Pallera & Schwartzberg, 2004).

The pre-engraftment phase of transplantation clearly represents many clinical challenges for oncology nurses, including infection, GI toxicities, myelosuppression, and renal and pulmonary complications. Recognition of these problems and appropriate intervention will potentially prevent significant harm to patients with MM during this phase of the transplantation process.

Phase 3: Engraftment

The time it takes for HSCs to migrate from the peripheral blood to the bone marrow and begin to grow is called blood count recovery or engraftment. Engraftment is established when the absolute neutrophil count is greater than 500 cells/dl for three consecutive days or greater than 1,000 cells/dl for one day, and platelets remain greater than 20,000 cells/dl, independent of platelet transfusions for at least seven days (DiPersio, Stadtmauer, et al., 2009). About three weeks (days +17 to +25) following infusion of HSCs, most acute toxicities, including myelosuppression related to the HDC, have resolved (Russell et al., 2013). Once the patient has no evidence of infection, has demonstrated engraftment, and establishes the ability to maintain oral hydration and nutrition, arrangements can be made for discharge (Pallera & Schwartzberg, 2004).

Phase 4: Post-Transplantation

As discussed in Miceli et al. (2013), the definition of post-transplantation has become less clear as more patients are being managed as outpatients during the acute phase of their transplantation course. For purposes of this discussion, *post-transplantation* refers to the time when patients leave the inpatient transplantation center and return to their home community. Additional discussion regarding the post-transplantation phase is included in Miceli et al (2013).

Phase 5: Late Effects

Advances in the science of HSCT, as well as advances in supportive care, have improved long-term survival of transplantation recipients. Survivors, however, are at risk for developing late complications secondary to pre-, peri-, and post-transplantation exposures. Those complications may lead to significant morbidity, mortality, and impaired quality of life (Majhail & Rizzo, 2013).

Long-term complications of AHSCT can be extensive and complicated. Every organ is potentially affected, and long-term follow-up guidelines are in place for screening and prevention of long-term transplantation complications. Some of the late complications include infection, as well as respiratory, ocular, oral, hepatic, renal, skeletal, neurologic, cardiac, and vascular complications (Majhail & Rizzo, 2013). Secondary primary malignancies also are a late complication for transplantation recipients (Thomas et al., 2012). Risk factors associated with the

Implications for Practice

- Consider all factors when determining patient eligibility for transplantation.
- Gain knowledge of supportive care strategies within each phase, including special considerations for allogeneic recipients, to increase the well-being and survival of patients.
- Anticipate short- and long-term side effects with prompt identification and intervention, when appropriate.

development of secondary malignancies include total body irradiation, primary disease, male gender, and pretransplantation therapy. Although many late complications are associated with allogeneic recipients, such as chronic graft-versus-host disease (cGVHD), autologous recipients are at risk for late complications as well (Majhail & Rizzo, 2013) (see Table 2).

Even long after the transplantation has taken place, the risk of infection in the patient is estimated to be 20 times higher than reported in the general population (Savani, Griffith, Jagasia, & Lee, 2011). Common bacterial infections include pneumococcal, streptococcal, and hemophilus organisms. Common viral infections include cytomegalovirus and reactivation of varicella zoster. Hepatitis B or C also can occur (Savani et al., 2011). Please refer to Miceli et al. (2013) of this supplement for more information and guidelines for treatment of infection.

Cardiovascular disease is another late complication of transplantation. Dyslipidemia, hypertension, diabetes, and kidney disease are associated with cardiovascular complications. The incidence of cardiovascular disease increases after transplantation and is thought to be related to GVHD, use of immunosuppressant agents, and the cumulative effects of chemotherapy. Other cardiovascular complications include cardiomyopathies, arrhythmias, or valvular dysfunction (Majhail et al., 2012; Savani et al., 2011).

Although guidelines are in place to monitor for long-term complications, barriers exist to implementing the guidelines (Burkhart, Wade, & Lesperance, 2013). Insurance coverage and insufficient reimbursement for screening appear to be major barriers. Lack of awareness and inadequate communication about the guidelines are other reasons for guideline nonadherence.

Implications for Nursing Practice

The role of HSCT in patients with MM is complex from the selection process to side effects and long-term management. Nurses play a critical role in the care of patients with MM because the nurse will anticipate and manage side effects and provide education and support to patients and caregivers. An enhanced understanding of the process is necessary to meet the needs of patients and caregivers.

Conclusion

HSCT remains an important treatment option for patients with MM. Eligibility is based on many factors and should be determined by the transplantation provider. Overall, the procedure is well tolerated in the autologous setting, with a low mortality rate in patients with MM (Kumar, 2009). Treatment-related mortality is much greater in the allogeneic setting; therefore, it is only recommended in the context of a clinical trial with a focus on individuals with high-risk disease characteristics. The goal of transplantation is to reinforce the response achieved by induction therapy and improve progression-free survival and overall survival. Acute and manageable side effects are an expected part of the transplantation process, with an anticipated period of post-transplantation recovery. Survivors of HSCT are at risk for developing complications for the remainder of their lives. Nurses must have adequate information to identify potential problems and implement strategies to manage the care of patients experiencing transplantation-related complications, both short- and long-term. Knowledge of the expected side effects and nursing interventions at each phase of the transplantation process will help patients and caregivers through this challenging process, improve outcomes, and enhance quality of life.

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TABLE 2. Screening and Preventive Practices for Long-Term Survivors After AHSCT

Organ	Screening Consideration
Cardiac or vascular	Education of heart-healthy lifestyle Endocarditis prophylaxis Early interventions for cardiovascular problems Monitor ferritin at one year for iron overload.
Endocrine or fertility	Monitor thyroid function test. Referral to appropriate specialist Birth control if indicated
Immune system	Immunization *Pneumocystis jiroveci* pneumonia and antiviral prophylaxis Monitor for encapsulated organisms.
Liver	Monitor liver function tests. Consider liver biopsy if indicated. Viral load monitoring and liver biopsy in patients with known hepatitis B or C Monitor serum ferritin at one year.
Musculoskeletal	Consider chronic graft-versus-host disease changes. Encourage activity. Vitamin D and calcium replacement Consider bisphosphonate therapy. Consider dual photon densitometry at one year.
Respiratory	Constant physical examination for pulmonary complications Smoking cessation
Ocular	Schedule regular ophthalmology examinations.
Oral	Schedule regular dental examinations. Ongoing oral examinations
Renal	Aggressively manage hypertension. Monitor renal function.
Secondary malignancies	Educate patients regarding risks adding to cancer diagnosis (e.g., smoking, sun exposure). Follow general population recommendations for cancer screening. Consider second malignancies based on symptoms. Monitor blood work on a regular basis, specifically complete blood cell levels.

AHSCT—autologous hematopoietic stem cell transplantation

Note. Based on information from Majhail & Rizzo, 2013; Savani et al., 2011.

References

Adel, N.G., Duck, E., Collum, K., Mccullagh, E., Reich, L., Landau, H., . . . Hassoun, H. (2011). Cost analysis of using plerixafor plus G-CSF versus cyclophosphamide plus G-CSF for autologous stem cell mobilization in multiple myeloma patients treated at Memorial Sloan-Kettering Cancer Center [Abstract 3537]. *ASH Annual Meeting Abstracts, 118,* 4059.

Amgen Inc. (2013). *Neupogen® (filgrastim)* [Package insert]. Retrieved from http://pi.amgen.com/united_states/neupogen/neupogen_pi_hcp_english.pdf

Antin, J.H., & Yolin Raley, D. (2009). Stem cell sources. In J.H. Antin & D. Yolin Raley (Eds.), *Manual of stem cell and bone marrow transplantation* (pp. 9–15). New York, NY: Cambridge University Press.

Bensinger, W.I. (2009). Role of autologous and allogeneic stem cell transplantation in myeloma. *Leukemia, 23,* 442–448.

Bevans, M., Tierney, D.K., Bruch, C., Burgunder, M., Castro, K., Ford, R., . . . Schmit-Pokorny, K. (2009). Hematopoietic stem cell transplantation nursing: A practice variation study [Online exclusive]. *Oncology Nursing Forum, 36,* E317–E325. doi:10.1188/09.ONF.E317-E325

Blombery, P., Prince, H.M., Worth, L.J., Main, J., Yang, M., Wood, E.M., & Westerman, D.A. (2011). Prophylactic intravenous immunoglobulin during autologous haematopoietic stem cell transplantation for multiple myeloma is not associated with reduced infectious complications. *Annals of Hematology, 90,* 1167–1172. doi:10.1007/s00277-011-1275-3

Burkhart, M.C., Wade, J., & Lesperance, V. (2013). Evidence-based guideline recommendations: Post-hematopoietic stem cell transplantation [Online exclusive]. *Clinical Journal of Oncology Nursing, 17,* E63–E67. doi:10.1188/13.CJON.E63-E67

Calandra, G., McCarty, J., McGuirk, J., Tricot, G., Crocker, S.A., Badel, K., . . . Bridger, G. (2008). AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: Compassionate use data. *Bone Marrow Transplantation, 41,* 331–338. doi:10.1038/sj.bmt.1705908

Cavo, M., Rajkumar, S.V., Palumbo, A., Moreau, P., Orlowski, R., Bladé, J., . . . Lonial, S. (2011). International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood, 117,* 6063–6073. doi:10.1182/blood-2011-02-297325

Chanan-Khan, A.A., & Giralt, S. (2010). Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. *Journal of Clinical Oncology, 28,* 2612–2624. doi:10.1200/JCO.2009.25.4520

Cooke, L., Grant, M., & Gemmill, R. (2012). Discharge needs of allogeneic transplantation recipients [Online exclusive]. *Clinical Journal of Oncology Nursing, 16,* E142–E149. doi:10.1188/12.CJON.E142-E149

DiPersio, J.F., Stadtmauer, E.A., Nademanee, A., Micallef, I.N., Stiff, P.J., Kaufman, J.L., . . . Calandra, G. (2009). Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood, 113,* 5720–5726.

DiPersio, J.F., Uy, G.L., Yasothan, U., & Kirkpatrick, P. (2009). Plerixafor. *Nature Reviews. Drug Discovery, 8,* 105–107.

Durie, B.G., Harousseau, J.L., Miguel, J.S., Bladé, J., Barlogie, B., Anderson, K., . . . Rajkumar, S.V. (2006). International uniform response criteria for multiple myeloma. *Leukemia, 20,* 1467–1473.

El-Cheikh, J., Crocchiolo, R., Furst, S., Stoppa, A.M., Ladaique, P., Faucher, C., . . . Blaise, D. (2013). Long-term outcome after allogeneic stem cell transplantation with reduced-intensity conditioning in patients with multiple myeloma. *American Journal of Hematology, 88,* 370–374. doi:10.1002/ajh.23412

Flomenberg, N., Devine, S.M., DiPersio, J.F., Liesveld, J.L., McCarty, J.M., Rowley, S.D., . . . Calandra, G. (2005). The use of AMD3100 plus G-CSF for autologous hematopoietic progenitor cell mobilization is superior to G-CSF alone. *Blood, 106,* 1867–1874.

Genzyme Corporation. (2010). *Mozobil® (plerixafor injection)* [Package insert]. Retrieved from http://www.mozobil.com/document/Package_Insert.pdf

Gertz, M.A., Wolf, R.C., Micallef, I.N., & Gastineau, D.A. (2010). Clinical impact and resource utilization after stem cell mobilization failure in patients with multiple myeloma and lymphoma. *Bone Marrow Transplantation, 45,* 1396–1403. doi:10.1038/bmt.2009.370

Giralt, S. (2012). Stem cell transplantation for multiple myeloma: Current and future status. *Hematology, 17*(Suppl. 1), S117–S120.

Giralt, S., Stadtmauer, E.A., Harousseau, J.L., Palumbo, A., Bensinger, W., Comenzo, R.L., . . . Durie, B.G. (2009). International Myeloma Working Group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100). *Leukemia, 23,* 1904–1912. doi:10.1038/leu.2009.127

Gopal, A.K., Harami, M., Mayor, J., Macebeo, M., Linenberger, M., Bensinger, W.I., & Holmberg, L. (2012). The effective use of plerixafor as a real-time rescue strategy for patients poorly mobilizing autologous CD34(+) cells. *Journal of Clinical Apheresis, 27*(2), 81–77. doi:10.1002/jca.21206

Harvey, R.D., Lonial, S., Renfroe, H., Sinha, R., Flowers, C.R., Lechowicz, M.J., . . . Kaufman, J.L. (2011). Temporal changes in plerixafor administration do not impact hematopoietic stem cell mobilization efficacy: Results of a prospective clinical trial [Abstract 2988]. Retrieved from https://ash.confex.com/ash/2011/webprogram/Paper35916.html

Hesketh, P.J., Batchelor, D., Golant, M., Lyman, G.H., Rhodes, N., & Yardley, D. (2004). Chemotherapy-induced alopecia: Psychosocial impact and therapeutic approaches. *Supportive Care in Cancer, 12,* 543–554.

Jakubowiak, A.J., Dytfeld, D., Griffith, K.A., Lebovic, D., Vesole, D.H., Jagannath, S., . . . Vij, R. (2012). A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood, 120,* 1801–1809. doi:10.1182/blood-2012-04-422683

Koreth, J., Stevenson, K.E., Kim, H.T., McDonough, S.M., Bindra, B., Armand, P., . . . Alyea, E.P., 3rd. (2012). Bortezomib-based graft-versus-host disease prophylaxis in HLA-mismatched unrelated donor transplantation. *Journal of Clinical Oncology, 30,* 3202–3208. doi:10.1200/JCO.2012.42.0984

Kumar, S. (2009). Stem cell transplantation for multiple myeloma. *Current Opinion in Oncology, 21,* 162–170. doi:10.1097/CCO.0b013e328324bc04

Kurtin, S., Lilleby, K., & Spong, J. (2013). Caregivers of multiple myeloma survivors. *Clinical Journal of Oncology Nursing, 17*(Suppl., 2), 25–32.

Laffan, A., & Biedrzycki, B. (2006). Immune reconstitution: The foundation for safe living after an allogeneic hematopoietic stem cell transplantation. *Clinical Journal of Oncology Nursing, 10,* 787–794. doi:10.1188/06.CJON.787-794

Lara, A.R., & Schwartz, M.I. (2010). Diffuse alveolar hemorrhage. *Chest, 137,* 1164–1171. doi:10.1378/chest.08-2084

Lilleby, K., Garcia, P., Gooley, T., McDonnell, P., Taber, R., Holmberg,

L., . . . Bensinger, W. (2006). A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. *Bone Marrow Transplantation, 37,* 1031–1035. doi:10.1038/sj.bmt.1705384

Lokhorst, H., Einsele, H., Vesole, D., Bruno, B., San Miguel, J., Pérez-Simon, J.A., . . . Bensinger, W. (2010). International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. *Journal of Clinical Oncology, 28,* 4521–4530. doi:10.1200/JCO.2010.29.7929

Majhail, N.S., Rizzo, J.D., Lee, S.J., Aljurf, M., Atsuta, Y., Bonfim, C., . . . Tichelli, A. (2012). Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplantation, 47,* 337–341. doi:10.1038/bmt.2012.5

Majhail, N.S., & Rizzo, J.D. (2013). Surviving the cure: Long term followup of hematopoietic cell transplant recipients. *Bone Marrow Transplantation*, 48, 1145–1151. doi:10.1038/bmt.2012.258

Martin, P.J., Schoch, G., Fisher, L., Byers, V., Anasetti, C., Appelbaum, F.R., . . . Sanders, J.E. (1990). A retrospective analysis of therapy for acute graft-versus-host disease: Initial treatment. *Blood, 76,* 1464–1472.

Mattson, M.R. (2007). Graft-versus-host disease: Review and nursing implications. *Clinical Journal of Oncology Nursing, 11,* 325–328. doi:10.1188/07.CJON.325-328

Micallef, I.N., Sinha, S., Gastineau, D.A., Wolf, R., Inwards, D.J., Gertz, M.A., . . . Kumar, S. (2013). Cost-effectiveness analysis of a risk-adapted algorithm of plerixafor use for autologous peripheral blood stem cell mobilization. *Biology of Blood and Marrow Transplantation, 19,* 87–93. doi:10.1016/j.bbmt.2012.08.010

Miceli, T., Lilleby, K., Noonan, K., Kurtin, S., Faiman, B., & Mangan, P.A. (2013). Autologous hematopoietic stem cell transplantation for patients with multiple myeloma: An overview for nurses in community practice. *Clinical Journal of Oncology Nursing, 17*(Suppl., 2), 13–24.

Moreau, P., Facon, T., Attal, M., Hulin, C., Michallet, M., Maloisel, F., . . . Harousseau, J.L. (2002). Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: Final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood, 99,* 731–735. doi:10.1182/blood.V99.3.731

National Cancer Institute. (2013). FDA approval for plerixafor. Retrieved from http://www.cancer.gov/cancertopics/druginfo/fda-plerixafor

Pallera, A.M., & Schwartzberg, L.S. (2004). Managing the toxicity of hematopoietic stem cell transplant. *Journal of Supportive Oncology, 2,* 223–237.

Palumbo, A., Bladé, J., Boccadoro, M., Palladino, C., Davies, F., Dimopoulos, M., . . . San Miguel, J. (2012). How to manage neutropenia in multiple myeloma. *Clinical Lymphoma, Myeloma and Leukemia, 12*(1), 5–11. doi:10.1016/j.clml.2011.11.001

Pasquini, M.C., & Wang, Z. (2011). Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2011. Retrieved from http://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/Pages/index.aspx

Potter, P., Eisenberg, S., Cain, K.C., & Berry, D.L. (2011). Orange interventions for symptoms associated with dimethyl sulfoxide during stem cell reinfusions: A feasibility study. *Cancer Nursing, 34,* 361–368. doi:10.1097/NCC.0b013e31820641a5

Richardson, P.G., Weller, E., Lonial, S., Jakubowiak, A.J., Jagannath, S., Raje, N.S., . . . Anderson, K.C. (2010). Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood, 116,* 679–686. doi:10.1182/blood-2010-02-268862

Rodriguez, A.L. (2010). Management and evaluation of patients receiving high-dose chemotherapy with stem cell transplantation. In J.D. Tariman (Ed.), *Multiple myeloma: A textbook for nurses* (pp. 155–172), Pittsburgh PA: Oncology Nursing Society.

Rosiñol, L., Oriol, A., Teruel, A.I., Hernández, D., López-Jiménez, J., de la Rubia, J., . . . Bladé, J. (2012). Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: A randomized phase 3 PETHEMA/GEM study. *Blood, 120,* 1589–1596.

Russell, N., Douglas, K., Ho, A.D., Mohty, M., Carlson, K., Ossenkoppele, G.J., . . . Chabannon, C. (2013). Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: Results of the prospective PREDICT trial. *Haematologica, 98,* 172–178. doi:10.3324/haematol.2012.071456

Savani, B.N., Griffith, M.L., Jagasia, S., & Lee, S.J. (2011). How I treat late effects in adults after allogeneic stem cell transplantation. *Blood, 117,* 3002–3007. doi:10.1182/blood-2010-10-263095

Solomon, S.R., Matthews, R.H., Barreras, A.M., Bashey, A., Manion, K.L., McNutt, K., . . . Holland, H.K. (2010). Outpatient myeloablative allo-SCT: A comprehensive approach yields decreased hospital utilization and low TRM. *Bone Marrow Transplantation, 45,* 468–475. doi:10.1038/bmt.2009.234

Sorror, M.L. (2010). Comorbidities and hematopoietic cell transplantation outcomes. *Hematology, 2010,* 237–246. doi:10.1182/asheducation-2010.1.237

Subramanian, A.K. (2011). Antimicrobial prophylaxis regimens following transplantation. *Current Opinion in Infectious Diseases, 24,* 344–349. doi:10.1097/QCO.0b013e328348b379

Sung, A.D., & Chao, N.J. (2013). Concise review: Acute graft-versus-host disease: Immunobiology, prevention, and treatment. *Stem Cells Translational Medicine, 2*(1), 25–32. doi:10.5966/sctm.2012-0115

Talamo, G., Rakszawski, K.L., Rybka, W.B., Dolloff, N.G., Malysz, J., Berno, T., & Zangari, M. (2012). Effect of time to infusion of autologous stem cells (24 versus 48 hours) after high-dose melphalan in patients with multiple myeloma. *European Journal of Haemoatology, 89,* 145–150. doi:10.1111/j.1600-0609.2012.01795.x

Thomas, A., Mailankody, S., Korde, N., Kristinsson, S.Y., Turesson, I., & Landgren, O. (2012). Second malignancies after multiple myeloma: From 1960s to 2010s. *Blood, 119,* 2731–2737.

Tuncer, H.H., Rana, N., Milani, C., Darko, A., & Al-Homsi, S.A. (2012). Gastrointestinal and hepatic complication of hematopoietic stem cell transplantation. *World Journal of Gastroenterology, 18,* 1851–1860. doi:10.3748/wjg.v18.i16.1851

Versluys, A.B., Rossen, J.W., van Ewijk, B., Schuurman, R., Bierings, M.B., & Boelens, J.J. (2010). Strong association between respiratory viral infection early after hematopoietic stem cell transplantation and the development of life-threatening acute and chronic alloimmune lung syndromes. *Biology of Blood and Marrow Transplantation, 16,* 782–791. doi:10.1016/j.bbmt.2009.12.534

Weinstock, D.M., Conlon, M., Iovino, C., Aubrey, T., Gudiol, C., Riedel, E., . . . Zuccotti, G. (2007). Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant. *Biology of Blood and Marrow Transplantation, 13,* 615–621.

Williams, S.F., Zimmerman, T., Grad, G., & Mick, R. (1993). Source of stem cell rescue: Bone marrow versus peripheral blood progenitors. *Journal of Hematotherapy, 2,* 521–523.