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The Role of High-Dose Chemotherapy Supported by Hematopoietic Stem Cell Transplantation in Patients With Multiple Myeloma:

Implications for Nursing

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Abstract

Multiple myeloma (MM), a neoplastic proliferation of plasma cells originating from the B-cell line, is associated with deleterious complications and poor outcomes. The failure of conventional combination chemotherapies to improve the overall survival of patients with MM has led to the use of high-dose chemotherapy supported by stem cell transplantation (SCT). Although several novel therapies have emerged since the late 1990s, their survival benefits are undetermined. High-dose chemotherapy with SCT provides better response rates compared to conventional chemotherapy and yields a trend toward greater survival benefits, especially with the use of a tandem (two successive) transplantation strategy. This article discusses standard SCT in patients with MM and some of the new transplantation strategies, including tandem autologous SCTs and reduced-intensity nonmyeloablative allogeneic SCT, and their implications for nursing.

The role of high-dose chemotherapy supported by stem cell transplantation (SCT) as a safe and effective therapy for patients with multiple myeloma (MM) is well established (Singhal, 2002). Since the 1990s, myeloma treatment advances have been made in the transplantation arena, but major challenges still lie ahead to improve overall survival (Barlogie et al., 2004). Several transplantation-related strategies have emerged, including tandem (i.e., two successive) autologous SCTs (ASCTs), autologous followed by allogeneic SCT, nonmyeloablative allogeneic transplantation, and sequential ASCTs followed by

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nonmyeloablative allogeneic transplantation, all in an effort to improve overall survival (Hari, Pasquini, & Vesole, 2006). Although several novel agents such as thalidomide, bortezomib, and lenalidomide have been effective in the treatment of MM, their impact on overall survival and quality of life in patients with MM is unclear (Tariman, 2005). This article discusses standard SCT in patients with MM, some of the newer transplantation strategies (e.g., tandem ASCT, reduced-intensity nonmyeloablative allogeneic SCT) and their implications for nursing.

Multiple Myeloma Overview

MM is the abnormal clonal proliferation of plasma cells originating from the B-cell line. An estimated 19,900 new myeloma cases and 10,790 deaths caused by the disease are anticipated in 2007 (Jemal et al., 2007). Many patients diagnosed with myeloma tend to be older (median age at diagnosis is 66), but some cases in patients younger than 40 have been reported (Kyle et al., 2003).

MM is a neoplastic growth from the single clone of a plasma cell that became aberrant and proliferated in an uncontrolled pattern with eventual accumulation in the bone marrow. Myeloma cells produce abnormal and dysfunctional monoclonal immunoglobulins (Igs) known as M proteins (Kyle, 2002). In contrast, normal plasma cells produce polyclonal Igs, a humoral immune response to a foreign antigen (Kyle & Lust, 1996). The Igs produced by myeloma cells break into pieces of heavy chains (i.e., IgG, A, or D) or kappa or lambda light chains. The IgD heavy chain rarely is seen, with an incidence of less than 1% of all myeloma cases (Kyle et al., 2003).

Monoclonal heavy-chain Igs in the blood can be measured with a serum protein electrophoresis test. The result of the test commonly is known as serum M spike, which usually is expressed in g/dl. Monoclonal light-chain Igs can be measured using urine protein electrophoresis; the urine M spike typically is expressed in mg over 24 hours (Rajkumar & Greipp, 2002). Approximately 77% of myeloma cases produce heavy-chain Igs (IgG or IgA), 20% produce only light-chain Igs (kappa or lambda), and about 3% do not produce any Ig at all (nonsecretory myeloma) (Kyle et al., 2003). Excessive M protein production may lead to renal failure, hyperviscosity syndrome, or recurrent infections requiring immediate interventions such as plasmapheresis or dialysis (Kyle, 2002).

MM is a disseminated bone marrow disease, occupying the long bones and the axial skeleton. Cytokines directly produced by myeloma cells often destroy bone tissues, causing bone pain, pathologic fractures, and, in some cases, spinal cord compression (Lokhorst, 2002). Unlike osteolysis, which is associated with other tumors that metastasize to the bone, myeloma-associated lytic lesions are unique because they do not repair, even after many years in complete remission. Lack of repair from osteolysis reflects a total loss of osteoblastic activity in areas of myeloma foci, apparently induced by myeloma (Epstein & Walker, 2006). In addition, the proliferation of abnormal plasma cells could lead to decreased bone marrow function, affecting the immune system's ability to fight against infectious agents. Thus, patients with MM usually succumb to a death that is strongly attributed to infection or sepsis (Kelleher & Chapel, 2002).

Patient Presentation and Assessment

Patients with MM often present with vague symptoms such as back pain, bone pain, fatigue, and anemia (Dvorak, 2006). In Kyle et al.'s (2003) review of 1,027 patients with MM, 58% presented with bone pain and 73% with anemia. Hypercalcemia and renal insufficiency along with bone pain and other clinical features of myeloma must alert clinicians to expediently rule out MM. MM must be distinguished from monoclonal gammopathy of undetermined significance or smoldering and indolent MM, which usually requires observation only until the disease transforms into symptomatic, active myeloma (Kyle et al., 2002; National Comprehensive Cancer Network, 2005).

Timely and effective control of the proliferation of myeloma cells is crucial to prevent serious end organ damage such as renal failure and bone destruction. Expedient diagnostic workup is paramount when myeloma is suspected, and the criteria for the diagnosis of MM must be established immediately. The minimal criteria for the diagnosis of MM are a bone marrow biopsy containing more than 10% plasma cells or a tissue biopsy showing plasmacytoma and the presence of serum M protein (usually more than 3 g/dl), urine M protein, or lytic bone lesions (Kyle, 2002; National Comprehensive Cancer Network, 2005).

Therapies

Conventional Chemotherapy Versus Single Autologous Stem Cell Transplantation

Systemic chemotherapy is the preferred initial treatment approach in patients with symptomatic, active myeloma. Patients with stage II or III disease according to the Durie-Salmon staging criteria usually require therapy (Durie & Salmon, 1975). The failure of conventional therapies to improve the overall survival of patients with MM has led to the use of high-dose chemotherapy with ASCT (Attal et al., 2003). A patient aged 70 or younger who is diagnosed with MM should be evaluated for eligibility for SCT (Kyle, 2002). Patients who are eligible for high-dose chemotherapy with ASCT should not receive alkylating agents such as melphalan prior to transplantation because of their potential to damage the stem cells and compromise adequate stem cell harvest (National Comprehensive Cancer Network, 2005).

Initial studies of high-dose chemotherapy with ASCT conducted in the late 1980s reported promising findings, with overall response rates as high as 74%, including 30%–50% complete remission with a mortality risk less than 10% (Barlogie & Gahrton, 1991; Gore et al., 1989). Three large randomized trials compared high-dose chemotherapy supported by single ASCT versus conventional chemotherapy. The studies showed that high-dose chemotherapy supported by single ASCT was superior to conventional chemotherapy in terms of response rates, event-free survival, and overall survival benefit (Attal et al., 1996; Child et al., 2003; Palumbo et al., 2004). Other randomized studies, however, did not show an overall survival advantage in the high-dose chemotherapy group (Barlogie, Kyle, et al., 2006; Blade et al., 2005; Fermand, Katsahian, et al., 2005). The conflicting findings may be attributed to trial designs, which frequently differ regarding patient age, timing of randomization, inclusion of nonresponders, maintenance therapies used, and frequency of

salvage transplantations (Barlogie et al., 2004). Figure 1 lists primary conventional chemotherapy regimens for patients with MM.

High-dose melphalan 200 mg/m² supported by ASCT is a well-established therapy for patients with MM (Gertz, Lacy, Dispenzieri, Hayman, & Kumar, 2006). The drug is considered the standard of care for patients younger than age 65 and select older patients of various ethnicities (Barlogie et al., 2004; Gertz et al.; Jantunen et al., 2006; Rajkumar, Gertz, Kyle, & Greipp, 2002; Saraf et al., 2006; Singhal, 2002). For patients who are not good candidates for transplantation, several other standard therapies are available, single agents such as bortezomib, thalidomide, and high-dose dexamethasone (Colson, Doss, Swift, Tariman, & Thomas, 2004; National Comprehensive Cancer Network, 2005; Tariman, 2003, 2005; Tariman & Estrella, 2005). Other combination therapies such as melphalan and prednisone, thalidomide and dexamethasone, or vincristine, doxorubicin, and dexamethasone (VAD) are used commonly (National Comprehensive Cancer Network). The combination of melphalan, prednisone, and thalidomide was reported as an alternative approach to high-dose chemotherapy with ASCT in older adult patients with previously untreated MM who are not good candidates for SCT because of adverse risk factors, including renal failure, cardiopulmonary disease, and advanced age with poor performance status (Palumbo et al., 2005).

Tandem Autologous Stem Cell Transplantation

A University of Arkansas group performed a historical control, pair-mate study comparing tandem high-dose chemotherapy with ASCT to Southwest Oncology Group patients treated with conventional VAD; vincristine, melphalan, cyclophosphamide, and prednisone; or vincristine, carmustine, doxorubicin, and prednisone combination chemotherapy (Barlogie et al., 1997). The study showed that tandem high-dose chemotherapy with ASCT induced higher partial response rates (85% versus 52%, $p < 0.0001$), better extended event-free survival (49 versus 22 months, $p = 0.0001$), and better overall survival (62+ versus 48 months, $p = 0.01$) when compared to conventional chemotherapy. The researchers concluded that dose intensification with double ASCT markedly augments tumor cytoreduction, affecting not only higher complete response rates but also significantly extending event-free survival and overall survival in previously untreated patients with MM (Barlogie et al., 1997). Since that study was conducted, the researchers have continued to lead innovations in tandem transplantations by combining novel agents such as thalidomide (total therapy 2 protocol) and bortezomib (total therapy 3 protocol) in a tandem transplantation program at the University of Arkansas Myeloma Institute (Barlogie et al., 2004; Barlogie, Tricot, et al., 2006). Patients who lack cytogenetic abnormalities such as deletion in chromosome 13 and hypodiploidy (i.e., less than 45 chromosomes) at baseline presentation had favorable outcomes, including a superior 12-year survival rate of 70% versus 30%, provided that they had a continuous four-year remission after five-year survival (Barlogie, Zangari, et al., 2006).

Single Versus Tandem Autologous Stem Cell Transplantation

Several randomized clinical trials have been performed to determine the superiority of tandem over single ASCT in patients with MM (see Table 1). In their trial, Attal et al.

(2003) enrolled 399 previously untreated patients younger than 60 years. Final analysis of the study with a median follow-up of 75 months in both arms showed that complete response or very good partial response was achieved by 42% of patients in the single transplantation group, compared to 50% of patients in the tandem transplantation group ($p = 0.10$). The probability of event-free survival for seven years after the diagnosis was 10% in the single transplantation group and 20% in the tandem transplantation group ($p = 0.03$). Significantly, the estimated seven-year overall survival rate was 21% in the single transplantation group and 42% in the tandem transplantation group ($p = 0.01$). Furthermore, the probability of surviving seven years among the patients who did not have a very good partial response was 11% and 43% in the single transplantation and tandem transplantation groups, respectively ($p = 0.0001$). Attal et al. (2003) concluded that tandem ASCT improves overall survival among patients with MM, especially those who did not achieve very good partial response after undergoing single ASCT. Fermand, Marolleau, et al. (2005) and Cavo et al. (2004) corroborated the findings of Attal et al. (2003); however, Cavo et al. expressed caution that mature data from a final analysis of the study must be reviewed before definite conclusions can be made concerning the impact of tandem ASCT on the outcomes of patients with MM. European Group for Blood and Marrow Transplant criteria were used for response assessment in all three studies (Blade et al., 1998) (see Table 2).

One prospective randomized trial comparing an intensive therapy versus double-intensive therapy supported by ASCT showed no overall survival benefit (Segeren et al., 2003). Attal et al. (2003) believed that the time for follow-up from the study, which ranged from 30–40 months, was not sufficient to draw definite conclusions. Segeren et al. also used an intermediate dose of melphalan at 70 mg/m^2 for two doses instead of the standard myeloablative regimen of 200 mg/m^2 (Barlogie et al., 2004). The late divergence of overall survival curves in Attal et al.'s (2003) trial after three to four years should caution against premature publication of randomized clinical trials addressing tandem versus single transplantation (Barlogie et al., 2004).

Based on the published results from randomized controlled trials by Attal et al. (2003); Fermand, Marolleau, et al. (2005); and Cavo et al. (2004), an increasing trend seems to exist toward better survival with tandem ASCT. A similar trend also is observed with nonrandomized published results of sequential ASCT (Barlogie, Zangari, et al., 2006).

Allogeneic Stem Cell Transplantation

Allogeneic SCT is the only proven potentially curative treatment for MM (Bensinger, 2005). Despite allogeneic SCT's curative potential, a very high treatment-related mortality of as much as 46% (Bensinger et al., 1996) remains the major limitation to wider clinical use of the modality. Sixty percent of treatment-related mortality within the first year was the result of regimen-related toxicity, graft-versus-host disease, hemorrhage, and infections, especially aspergillus (Bensinger). Because of the high mortality risk, allogeneic SCT usually is offered only to patients younger than age 55 who have failed conventional chemotherapies.

Allogeneic SCT can induce long-term disease-free survival and reduce relapse risk (Gahrton et al., 2001), most likely because of the unique capacity of donor lymphocytes to recognize and kill recipient plasma cells, known as graft-versus-myeloma effect (Corradini et al.,

2003). Progress in allogeneic SCT has been significant, with a reduction in transplantation-related mortality from 46%–30% observed in Gahrton et al.'s study. With mortality risk still at 30%, clinical trials with better patient selection, new conditioning methods, and the combination of allogeneic SCT with novel targeted drugs such as bortezomib and lenalidomide are needed to further define the role of allogeneic SCT in patients with MM (Gahrton, 2005). Advances in supportive care and a decrease in transplantation-related mortality warrant a reexamination of the use of conventional myeloablative allogeneic SCT, especially among patients with high-risk, aggressive myeloma (Hari et al., 2006).

Reduced-Intensity Nonablative Allogeneic Stem Cell Transplantation

The use of nonmyeloablative reduced-intensity conditioning (i.e., “mini-allogeneic” transplantation) has significantly decreased treatment-related mortality; however, the relapse rate is higher than with standard conditioning, and therefore, no significant improvement in overall survival has been seen (Gahrton, 2005). Reduced-intensity conditioning regimens are designed for immunosuppression rather than reduction of myeloma tumor burden. The goal of the approach is to establish consistent donor engraftment while minimizing toxicity and damage to normal host tissues (Bensinger, 2005). In addition, low-intensity immunosuppression should minimize or eliminate the period of severe pancytopenia that frequently occurs after high-intensity conditioning.

A small study (N = 22) showed that allogeneic SCT using a reduced-intensity regimen for patients with MM who have failed conventional chemotherapy could achieve an estimated 25.5% probability of two-year overall survival (Einsele et al., 2003). Furthermore, researchers found that chemorefractory disease prior to allogeneic SCT ($p = 0.0182$) and the absence of chronic graft-versus-host disease ($p = 0.069$) were associated with decreased event-free survival. The study suggests that the approach may be beneficial when attempted before the development of chemorefractory disease. Another study using reduced-intensity conditioning regimens showed promising results among 31 patients with MM (Badros et al., 2002). Thirty patients had received one or more ASCT with high-dose melphalan. At a median follow-up of six months, 19 (61%) of 31 patients achieved complete response or near complete response. Twelve patients (39%) died: three because of progressive disease, three of early treatment-related mortality (within 100 days of transplantation), and six from late treatment-related mortality (after post-transplantation day 100). The median overall survival was 15 months (Badros et al.).

Further refinements of mini-allogeneic SCT procedures hopefully will make them more widely used, especially after promising results are demonstrated in high-risk patients, such as chemorefractory patients with poor prognostic factors (Barlogie et al., 2004). Sequential ASCT followed by nonmyeloablative allogeneic SCT also is being explored.

Nursing Implications

Pretransplant Patient Evaluation

Many life-threatening complications are associated with SCT, necessitating thorough evaluation of patients to determine eligibility for transplantation. Special attention is given to determination of organ dysfunction that could increase regimen-related toxicity or

exclude patients from myeloablative transplantation (Flowers & Sullivan, 2004). Figure 2 outlines suggested patient evaluation requirements prior to SCT. General considerations for eligibility include determining that patients have chemotherapy-sensitive disease, adequate organ function, and no life-threatening viral exposures or comorbidities (Niess & Duffy, 2004). In addition, performance status, financial resources (i.e., insurance coverage benefits), and family and caregiver support and commitment are important considerations prior to admission for SCT. Oncology nurses should ensure that pretransplant evaluations are completed. All critical findings such as abnormal echocardiogram (poor ejection fractions), poor pulmonary function test results, renal insufficiency (creatinine more than 2.0 g/dl), and any other concerns that could compromise patient safety should be discussed with the transplantation team. Pretransplantation nursing responsibilities include assessing patients' physical condition and performance status, evaluating patients' laboratory results with referral of abnormal results to a physician, reviewing patients' psychological condition and support systems to assess any psychosocial issues that may affect recovery and care after discharge, and educating patients and families or caregivers about the SCT collection process, SCT procedure, discharge planning, and home care.

Stem Cell Mobilization

The number of circulating stem cells in the blood is low compared with the number of stem cells in the bone marrow. Mobilization is a technique that is used to increase the number of circulating stem cells in the peripheral blood. Stem cell mobilization is achieved using chemotherapy (chemomobilization), growth factors (G-mobilization), or both. Chemotherapy followed by use of a growth factor could increase the number of circulating progenitor cells by approximately 60-fold, whereas use of a growth factor alone can result in an 18-fold increase in circulating stem cells. Chemomobilization with growth factor mobilization is the most common method of stem cell collection; the synergistic technique reduces the number of apheresis needed to collect adequate cells for hematopoietic reconstitution. In some patients, however, growth factor mobilization is preferred when chemotherapy for further reduction of myeloma burden is not a critical need prior to stem cell collection (i.e., patient's myeloma burden is significantly reduced by primary induction chemotherapy). Growth factor mobilization alone can yield an adequate number of stem cells required for transplantation. Optimal mobilization techniques have not yet been determined, but combination agents of chemotherapy and colony-stimulating factors are believed to give optimal cell yield. The two most common agents for stem cell mobilization are cyclophosphamide 2–4 g/m² and granulocyte macrophage–colony-stimulating factors or granulocyte colony-stimulating factors (Singhal, 2002).

A human leukocyte antigen–matched sibling or unrelated donor can donate stem cells to patients for allogeneic SCT. Donors do not require chemotherapy for mobilization. G-mobilization is the only method applicable to collect adequate donor stem cells.

Mobilization protocols vary among institutions and are based on a number of factors, including patient disease status, medical history, age, current health status, previous response to chemotherapy, and ability to tolerate the adverse effects of multiple doses of chemotherapy. Nurses are challenged to prevent complications from and alleviate the

adverse effects of chemotherapy and colony-stimulating factors in stem cell mobilization (see Table 3). Nursing management involves patient preparation, education, assessment, and management of anticipated symptoms.

Stem Cell Collection

Successful blood and marrow transplantation, both autologous and allogeneic, requires the infusion of a sufficient number of hematopoietic progenitor or stem cells capable of homing in the marrow cavity and regenerating a full array of hematopoietic cell lineages in a timely fashion (Cottler-Fox et al., 2003). Stem cells may be collected from the bone marrow, peripheral blood, or umbilical cord blood. Currently, stem cells often are collected through the peripheral blood using apheresis. Physician orders for stem cell collection must be obtained once eligibility criteria for SCT are met. Prior to stem cell collection, a multipurpose double- or triple-lumen vascular access device is placed. Care of the vascular access device to prevent line site infection and occlusion should be observed meticulously. Sterile dressing changes should follow each apheresis procedure, and the central line must be heparinized per institution protocol.

Once mobilization is completed, stem cell collection usually is scheduled when the white blood count starts to recover from neutropenic nadir 10–14 days after chemotherapy. When chemotherapy is used for mobilization, the white blood count must be greater than 10,000 cells/mm³ with clear evidence of rising counts prior to stem cell collection. If a growth factor is used to stimulate neutrophil production, a count exceeding 20,000 cells/mm³ usually indicates that a patient is ready for apheresis (Wujcik, 2005). The most commonly used surrogate marker for hematopoietic progenitor or stem cells is the cell surface marker CD34, identified in the clinical laboratory by flow cytometry (Cottler-Fox et al., 2003). The number of the CD34+ cells in the peripheral blood should be assessed to determine the best time to start the collection. Clinical studies have shown that infusion of at least 2×10^6 CD34(+) cells/kg recipient body weight results in reliable engraftment as measured by recovery of adequate neutrophil and platelet counts approximately 14 days after transplant (Cottler-Fox et al.). Basics of stem cell collection are outlined in Figure 3. Nursing responsibilities for the stem cell collection process include verifying patients' height and weight, verifying that informed consent is signed, verifying the patency of the central venous access device, checking for a physician order for apheresis, monitoring the chemistry panel (electrolytes are replaced as needed per physician's orders), and monitoring the complete blood count. Platelet and packed red blood cell transfusion may be required prior to apheresis; parameters usually are institution specific, although some institutions require a platelet count of $40 \times 10^9/L$ and hemoglobin of 9 g/dl (or a spun hematocrit of 27%) (Northwestern Memorial Hospital, 2001).

During stem cell collection, patients must be assessed for potential side effects associated with the procedure, such as fluid and electrolyte imbalances and hypothermia. Sterile technique should be practiced during the care of central line catheters. Nurses also should reinforce transplant-related patient teachings such as neutropenic and thrombocytopenic precautions. A sibling or unrelated donor typically needs the same nursing care as the patient

during the collection process. Table 4 outlines the common side effects of stem cell collection and suggested nursing interventions.

Stem Cell Processing and Cryopreservation

After collection, stem cells are tested for sterility and infectious diseases and then typed. The screening and testing procedures help to minimize the risk of transmission of infectious agents, such as HIV-1, HIV-2, hepatitis B, hepatitis C, human T-cell lymphocytic virus-I, human T-cell lymphocytic virus-II, cytomegalovirus, and syphilis (American Association of Blood Banks et al., 2005).

After testing, excess plasma is removed from the apheresis product by centrifugation. The concentrated stem cells then are diluted with an equal volume of human serum albumin solution supplemented with a cryopreservative. Cryopreservation techniques allow for optimal preservation of hematopoietic function and viability of cells (Calmels et al., 2003). Prior to storage, 10% dimethyl sulfoxide (DMSO) is added to the stem cells as a cryoprotectant. DMSO stabilizes cell membranes under rapidly changing conditions and prevents intracellular ice crystal formation during freezing and heat release throughout the period of phase transition, preserving stem cell integrity (Calmels et al.; Windrum, Morris, Drake, Niederwieser, & Ruutu, 2005). Stem cells are cryopreserved and stored in a freezer at a temperature of -80°C to -196°C (Schmit-Pokorny, 2004). Allogeneic stem cells from some healthy donors do not require cryopreservation when donor cells are infused immediately following collection and processing. Donor cells that are not infused immediately may be stored in a refrigerator at 4°C and infused the day following collection (Schmit-Pokorny). If allogeneic stem cells are for later use, similar cryopreservation techniques with DMSO are followed. Oncology nurses and stem cell laboratory personnel must ensure that stem cell collection bags are labeled properly with the patient's or donor's identifier. Oncology nurses should provide patients with post-stem cell collection instructions (e.g., the need for further apheresis, scheduled clinic visits, laboratory monitoring by a homecare nurse or through an out-patient clinic), provide patients and caregivers with instructions on central venous catheter care, provide patients and families or caregivers with guides for calling the healthcare team, assess the knowledge of patients and families or caregivers regarding the SCT reinfusion process, and reinforce teaching as needed.

During Stem Cell Transplantation

The myeloablative conditioning regimen that commonly is used in patients with MM is melphalan 200 mg/m^2 over one day or melphalan 100 mg/m^2 over two days. Other regimens such as melphalan plus total body irradiation, busulfan-based regimens, high-dose etoposide, and holmium 166-labeled phosphonate are less favored because of increased toxicities with no added benefit (Tariman & Estrella, 2005). Premedications usually are given prior to high-dose melphalan. SCT or reinfusion is performed 24 hours after high-dose melphalan administration and is considered as day 0 of SCT. The stem cell reinfusion is performed in the patient's room or outpatient suite. Figure 4 describes the stem cell reinfusion procedure.

Patients should be monitored carefully during the stem cell re-infusion procedure because the cryoprotectant DMSO is known to have toxic effects (Windrum et al., 2005). Reported adverse reactions to DMSO include nausea and vomiting, abdominal cramps, chills, dyspnea, hypotension or hypertension, bradycardia, arrhythmias, alveolar hemorrhage, acute renal failure, and cardiac or respiratory arrest (Alessandrino et al., 1999; Calmels et al., 2003; Hoyt, Szer, & Grigg, 2000; Windrum et al.). Aside from toxic reactions to DMSO, acute hemolytic reactions caused by donor-recipient major ABO incompatibility and febrile non-hemolytic reactions may occur.

During reinfusion, nurses should frequently monitor vital signs, including pulse oximetry, and assess for signs and symptoms of fluid overload, adverse reactions to DMSO, acute hemolytic reactions (e.g., chills, dyspnea, chest or lower back pain, facial flushing, rapid and labored respirations), and allergic or anaphylactic reactions (e.g., wheezing, urticaria, pruritus, severe dyspnea, hypotension). If adverse reactions are noted, a nurse should slow or temporarily stop the infusion, notify the physician immediately, administer medications as ordered (e.g., corticosteroids, antihistamines, diuretics, epinephrine, vasopressor agents), and administer oxygen therapy as needed. In the event of respiratory or cardiac arrest, follow institutional policies and procedures on aggressive life support.

After reinfusion, nurses must inform patients and their families that the urine may be pink or red-tinged for 24–48 hours. In addition, patients may notice a garlic taste in the mouth. Nurses should discuss with patients what to expect over the next two weeks, including pancytopenia with frequent blood product support, mucositis and pain management, and engraftment. Successful engraftment is evident usually around day 10 of SCT. Full recovery of blood cell counts is expected after two weeks, but, in some cases, it may take as many as three weeks.

After Stem Cell Transplantation

Patients should be assessed for fatigue, anxiety, pain, insomnia, appetite loss, mucositis, nausea, and vomiting, which are among the most commonly reported symptoms during SCT (Hacker, 2003). Symptoms can affect patients' quality of life (Hann et al., 1999; Marks, Gale, Vedhara, & Bird, 1999; McQuellon et al., 1996). Oncology nurses are in a key position to facilitate ongoing assessments of common symptoms and initiate evidence-based nursing interventions.

Before patients are discharged from a transplantation facility, nurses should give them comprehensive medication instructions, including the dose, frequency, and length of use. Patients' homes should be evaluated prior to discharge for appropriateness for receiving post-transplant care. Support systems and primary caregivers should be identified clearly. Patients should receive clearly written instructions regarding the frequency of laboratory tests, physician visits and follow-up, and disease restaging procedures. Oncology nurses need to continue to assess patients' quality-of-life issues after transplantation to determine whether patients are experiencing significant deficits in physical, social, emotional, or spiritual domains. Despite all of the quality-of-life issues reported by patients, 80%–90% have reported that they would choose to undergo a transplantation again (Claisse, Hirsch, & Gluckman, 1994; Tariman, Paice, Mehta, Duffey, & Singhal, 2006).

Conclusion

The complexity of care for patients with MM who undergo SCT, whether it is a single (autologous or allogeneic) or tandem (sequential autologous or autologous followed by ablative or nonmyeloablative allogeneic) transplantation, requires clinical nursing expertise, critical technical competencies, and a comprehensive knowledge base. Nurses provide complex assessments, thoughtful care planning, and patient management throughout the SCT continuum. Oncology nurses must continue to stay informed about the various regimens and transplantation strategies for MM to deliver high-quality nursing care and provide for the best patient experience. Finally, oncology nurses play important roles before, during, and after SCT that ensure patients' safety and comfort.

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At a Glance

- Multiple myeloma is associated with deleterious complications and poor outcomes. Patients diagnosed with myeloma tend to be older, with a median age at diagnosis of 66 years.
- Better overall survival has been reported in patients who are aged 60 or younger and treated with tandem autologous stem cell transplantation (SCT).
- Oncology nurses play a key role in ensuring the safety and delivery of high-quality care before, during, and after SCT.

- Melphalan and prednisone
- Vincristine, doxorubicin, and dexamethasone
- High-dose pulsed dexamethasone
- Thalidomide and dexamethasone
- Liposomal doxorubicin, vincristine, and dexamethasone
- Melphalan, prednisone, and thalidomide

Figure 1. Primary Conventional Chemotherapies for Multiple Myeloma

Note. Based on information from National Comprehensive Cancer Network, 2005; Palumbo et al., 2005.

<p>Core Requirements of the Pretransplantation Evaluation</p> <ul style="list-style-type: none"> • Review of records and completed history and physical examination • Review of original diagnostic slides to confirm the primary disease • Bone marrow aspirate and core biopsies <ul style="list-style-type: none"> – Aspirate for flow cytometry to determine clonality – Aspirate for cytogenetics or fluorescence in situ hybridization study, such as deletion of chromosome 13 – Plasma cell labeling index to determine proliferative rate of plasma cells • Radiologic staging studies • Skeletal survey • Magnetic resonance imaging scan of the skull, spine, and pelvis, especially in patients with cord compression or large lesions in the skull or pelvis found in x-rays <p>Multiple Myeloma–Specific Tests</p> <ul style="list-style-type: none"> • Quantitative immunoglobulin • Serum and 24-hour urine protein electrophoresis • Serum and urine immunofixations • C-reactive protein and serum beta-2-microglobulin <p>Laboratory Tests</p> <ul style="list-style-type: none"> • Complete blood count with platelets and reticulocyte counts • Chemistry panel, including electrolytes, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransaminase, aspartate aminotransferase, bilirubin, lactic dehydrogenase, cholesterol, triglycerides, and immunoglobulin levels • ABO, Rh typing, direct Coombs test • Follicle-stimulating hormone, luteinizing hormone, estradiol, and human chorionic gonadotropin levels (female patients) • Testosterone total and free levels (male patients) • Blood-specific disease markers • Human leukocyte antigen typing (allogeneic transplant) <p>Infectious Disease Testing</p> <ul style="list-style-type: none"> • Hepatitis screening (non-A, non-B, A, B, C) • HIV antibody test • Cytomegalovirus titer • Herpes-varicella-zoster virus • Epstein-Barr virus • Toxoplasmosis titer • Syphilis serology <p>Procedures</p> <ul style="list-style-type: none"> • Chest x-ray • Dental x-ray • Electrocardiogram • Cardiac ejection studies • Pulmonary function tests <p>Special Consultation</p> <ul style="list-style-type: none"> • Radiation oncology • Social services • Nutrition • Blood center <p>Informed Consent</p>

Figure 2. Evaluation of Patients With Multiple Myeloma Prior to Autologous Stem Cell Transplantation

Note. Based on information from Foundation for the Accreditation of Hematopoietic Cell Therapy, 1997; Kapustay & Buchsel, 2005; National Comprehensive Cancer Network, 2005; Niess & Duffy, 2004.

- A double- or triple-lumen apheresis catheter is placed.
- Outpatient or inpatient procedure
- Duration depends on blood flow and total volume for apheresis.
- 12–15 liters are processed over two to four hours.
- Collection occurs over an average of four days.
- Whole blood enters the machine from one lumen and is mixed with an anticoagulant.
- The blood is separated into fluid and cellular components using a cell separator.
- Centrifugal action separates the highest density (red blood cells) and lowest density cells (plasma).
- Stem cells are found in the middle layer.

Figure 3. Basics of Stem Cell Collection

Note. Based on information from Letheby et al., 2005; Schmit-Pokorny, 2004.

1. Verify consent.
2. Administer prehydration and premedication as ordered.
3. Verify central line patency.
4. Ensure oxygen and suction set-up are assembled and working properly.
5. Ensure that emergency medications are available at the bedside.
6. Check the central line for blood return.
7. Attach infusion tubing to the patient's central line.
8. The RN and stem cell laboratory technologist should verify the patient's name, medical record number, and product number prior to thawing the cells.
9. Stem cells are thawed in a water bath.
10. The RN and stem cell laboratory technologist again verify the following patient information prior to stem cell transfusion.
 - a. Patient's name
 - b. Medical record number
 - c. Product number
 - d. Product type
 - e. Product expiration
 - f. Patient ABO/Rh factor
 - g. Product ABO/Rh factor
11. The RN begins to reinfuse the stem cells.
12. Vital signs are taken and recorded frequently during the reinfusion.
13. At the end of the reinfusion, the RN documents the number of cells infused and volume, as well as signs and symptoms of adverse events, including interventions, if needed.
14. The RN continues to monitor the patient for at least one hour after reinfusion.

Figure 4. Stem Cell Reinfusion Procedure

Note. Based on information from American Association of Blood Banks et al., 2005.

Table 1
Summary of Clinical Trials of Single Versus Tandem ASCT in Patients With Multiple Myeloma

STUDY	N	MEAN AGE (YEARS)	MEAN FOLLOW-UP (MONTHS)	MEDIAN EFS		MEDIAN OS		COMMENTS
				%	p	RESPONSE (%)	%	
Attal et al., 2003								
Single ASCT	199	52	75	10	0.03	42 (CR)	21	EFS and OS were measured at seven years.
Tandem ASCT	200	52	75	20		50 (CR)	42	
Cavo et al., 2004								
Single ASCT	115	53	45	–	0.000001	35 (CR)	44	EFS was 12 months longer in patients who failed to achieve CR or NCR. OS was measured at six years and was extended in
Tandem ASCT	113	53	54	–		48 (NCR)	63	patients who failed to achieve CR or NCR (p = 0.04).
Fermand, Marolleau, et al., 2005								
Single ASCT	197	50	73	–	0.11	37 (VGPR)	–	VGPR was measured at six months. Mean EFS was 31 and 36 months for single and tandem ASCT, respectively. Median OS was 57 and 75 months for single and tandem ASCT, respectively.
Tandem ASCT	196	50	73	–		38 (VGPR)	–	

ASCT—autologous stem cell transplantation; CR—complete response; EFS—event-free survival; NCR—near complete response; OS—overall survival; VGPR—very good partial response

Table 2

European Group for Blood and Marrow Transplant Criteria for Response to Therapy

RESPONSE CRITERIA COMPONENT	COMPLETE RESPONSE	NEAR COMPLETE RESPONSE	PARTIAL RESPONSE	MINIMAL RESPONSE
M protein	Absent in serum and urine	Absent in serum and urine	50% reduction in serum and 90% reduction in urine (or absolute value < 200 mg over 24 hours)	25% reduction of serum para-protein and 50% reduction in urine paraprotein
Immunofixation test	Negative	Positive	Not required	Not required
Bone marrow biopsy	< 5% plasma cells	< 5% plasma cells	Not required	Not required
Bone lytic lesions	Stable or improved	Stable or improved	Stable or improved	Stable or improved
Plasmacytomas	Absent	Absent	Decreased by 50%	Decreased by 25%

Note. Based on information from Blade et al., 1998.

Table 3

Common Complications Associated With Chemomobilization and Transplantation

COMPLICATION	CAUSE	SYMPTOMS	NURSING INTERVENTIONS
Infection (<i>Staphylococcus aureus</i>)	Neutropenia from high-dose chemotherapy conditioning	Fever, shaking, chills, and hypotention	<ul style="list-style-type: none"> Teach patients about neutropenic precautions and how to take medications, recognize signs and symptoms of infection, and administer prophylactic antimicrobials (e.g., acyclovir, ciprofloxacin, fluconazole). Teach patients about institutional procedures that will occur in the event of febrile neutropenia (e.g., cultures of blood, urine, stool, throat, and central venous catheter exit sites; chest x-ray). Prescribe antibiotics promptly.
Hemorrhagic cystitis	Exposure of bladder lining to cyclophosphamide metabolites	Hematuria or blood clots in urine	<ul style="list-style-type: none"> Aggressively hydrate patients prior to, during, and after chemotherapy. Administer mensa. Perform a urine dip-test every eight hours at the start of and after chemotherapy. Strictly monitor input and output; teach patients about the importance of frequent voiding.
Bleeding	Pancytopenias or loss of platelets resulting from toxic effects of chemotherapy-induced mobilization	Shortness of breath, headache, blurred vision, petechia, ecchymosis, bleeding or oozing from any orifice or injection site; most frequent sites of bleeding are mucous membrane, intracranial area, skin, and gastrointestinal, respiratory, and genitourinary systems.	<ul style="list-style-type: none"> Institute bleeding precautions. Closely monitor platelet count and vital signs. Perform a urine dip-test and occult for stool blood. Avoid invasive procedures. Discontinue drugs that interfere with platelet production or function. Transfuse platelets or red blood as indicated. Maintain integrity of skin and mucous membranes. Avoid increased intracranial pressure.
Malnutrition or dehydration	High-dose chemotherapy conditioning (busulfan, melphalan, thiotepa) causing nausea, vomiting, diarrhea, constipation, and mucositis	Myriad symptoms resulting from a complex neurophysiologic phenomenon: hypovolemia, hypotension, tachycardia, tachypnea, weight loss, and anorexia	<ul style="list-style-type: none"> Administer medications as ordered (e.g., decadron, granisetron hydrochloride, ondansetron, lorazepam, diphenhydramine hydrochloride, stool softener, milk of magnesia for constipation). Offer cold, small, bland liquid meals. Sour foods are sometimes tolerated. Decrease external stimuli. Monitor weight, intake and output, and nutritional status.

COMPLICATION	CAUSE	SYMPTOMS	NURSING INTERVENTIONS
Fatigue	Pancytopenia resulting from high-dose chemotherapy	Patient report of excessive tiredness or generalized body weakness	<ul style="list-style-type: none"> • Encourage a balance of rest and activity. • Encourage light to moderate exercise. • Administer blood products as indicated.
Veno-occlusive disease	High-dose chemotherapy	Ascites, weight gain, confusion, and jaundice	<ul style="list-style-type: none"> • Weigh the patient twice a day. • Measure abdominal girth. • Offer supportive care. • Administer diuretics as ordered.
Mucositis	High-dose chemotherapy	Pain, facial and throat swelling, airway occlusion, anorexia, difficulty swallowing and talking, and erythema, edema, and erosions of the mucosal lining	<ul style="list-style-type: none"> • Encourage patients to perform frequent mouth care with use of a soft toothbrush, floss, or a toothette. • Encourage patients to use bland rinses with a saline or sodium bicarbonate solution. • Patients should avoid mouthwash containing alcohol.
Flulike syndrome	Mobilization with colony-stimulating factors	Fevers, chills, arthralgias, myalgias, chills, headaches, and malaise	<ul style="list-style-type: none"> • Administer analgesics (e.g., acetaminophen)
Skin toxicity	Mobilization with colony-stimulating factors	Indurated skin rash	<ul style="list-style-type: none"> • Assess the injection site daily. • Apply topical cortisone as indicated.

Note. Based on information from Kapustay & Buchsel, 2005; McAdams & Burgunder, 2005.

Table 4

Common Side Effects of Stem Cell Collection and Nursing Interventions

SIDE EFFECT	CAUSE	INTERVENTION
Hypocalcemia	Sodium citrate used to prevent clotting binds ionized calcium.	Administer oral calcium supplementation and check the ionized calcium level. IV supplementation is needed for severe hypocalcemia with life-threatening symptoms such as decreased myocardial contractility leading to congestive heart failure, hypotension, and bradycardia.
Hypovolemia	Extracorporeal volume is greater as whole blood is processed.	Monitor blood pressure, and administer IV fluids as ordered.
Thrombocytopenia	Collection of platelets in product	Monitor the platelet level. Apheresis may not commence if the platelet level is less than 20,000/dl. Monitor the patient for signs and symptoms of bleeding (e.g., bleeding at central line insertion site, nose bleed). Administer platelets as ordered.
Chilling	Cooling of blood while circulating in apheresis machine	Provide the patient with a warmed blanket. Monitor the room temperature and adjust accordingly.
Severe headache	Side effect of growth factor	Administer a pain reliever (e.g., acetaminophen) as ordered.
Prolonged cytopenia	Side effect of previous chemotherapy	Support growth factors, transfuse blood and blood product as needed, and begin neutropenic precautions if indicated.

Note. Based on information from Schmit-Pokorny, 2004.