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The Roles of Nurses in Hematopoietic Cell Transplantation for the Treatment of Leukemia in Older Adults

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ABSTRACT

Objective: To review and summarize nurses' roles in the care of the older adult undergoing an allogeneic hematopoietic cell transplant (HCT) for the treatment of leukemia.
Data Sources: Published literature indexed in PubMed, CINAHL, textbooks, and clinical expertise.
Conclusion: Nurses are a vital component of the highly specialized care delivered before, during, and after an allogeneic HCT.
Implications for Nursing Practice: Nurses who are prepared for the complex HCT care trajectory will be able to optimally meet the complex needs of the older adult patient and their caregiver(s).

Introduction

An allogeneic hematopoietic stem cell transplantation (HCT) remains the principal curative therapy for malignant hematologic conditions, including acute myeloid leukemia and acute lymphocytic leukemia.[1–3] Historically, older adults (ie, age ≥ 65) had not been considered good candidates for HCT because age is a reliable prognostic indicator of transplant success.[4] However, recent data from the Center for International Blood and Marrow Transplant Research support the use of HCT in fit older adults. The number of older adults who received allogeneic HCT has nearly doubled over the last decade.[4,5]

Among older adults, survival after 2 or more years following allogeneic HCT is improving, potentially because of better HLA matching of unrelated graft donors, improved prophylactic regimens for graft-versus-host disease (GVHD), and less toxic (ie, reduced intensity) conditioning regimens.[6] One study estimated the cumulative incidences of 2-year and 5-year relapse-free survival among older patients with acute myeloid leukemia who received allogeneic HCT to be approximately 47% and 35%, respectively.[7] Another study estimated the 3-year overall survival rates for older patients with acute myeloid leukemia receiving allogeneic HCT with matched sibling donors and matched unrelated donors were 55% and 45%, respectively.[8] Although these survival rate estimates are not excellent, older adults with acute leukemias may add meaningful, disease-free years to their lives following allogeneic HCT.

Nurses who work in transplant and cellular therapy (TCT) and hematology/oncology settings play a vital role in the assessment, delivery of interventions, and education during the HCT trajectory. Patient acuity in TCT settings is high because of several factors, including management of multiple intravenous (IV) medications, parenteral nutrition, psychosocial factors, and labile patient stability throughout transplant.[9] Nurses who are new to TCT settings will benefit from understanding the complex nature of HCT in older adult patients, including: geriatric oncology considerations; the common acute symptoms and outcomes of HCT; and the transition to survivorship and palliative care.

The purpose of this article is to review and summarize the various roles of nurses during the care of older adult patients being treated for leukemia with HCT, by summarizing the current published, peer-reviewed literature. The authors retrieved the literature for this review through PubMed, CINAHL, textbooks, and inpatient clinical practice guidelines.

Conditioning Considerations for Older Adults Receiving HCT

There are two kinds of hematopoietic cell transplantations: autologous and allogeneic transplants.[10,11] Table 1 provides a brief overview of HCT classifications, malignant diseases treated, and donor source. For the remainder of this article, we will focus on the context of TCT nursing for allogeneic HCT.

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Table 1
Classifications of hematopoietic cell transplantation.

Classification	Description	Malignant diseases treated	Donor
Autologous	Infusion of the patient's harvested hematopoietic stem cells from marrow collection or peripheral blood prior to receiving induction chemotherapy	Non-Hodgkin lymphoma Hodgkin lymphoma* Multiple myeloma	Patient
Allogeneic	Infusion of hematopoietic stem cells from a donor that were obtained by collecting peripheral blood, marrow, or umbilical cord blood	Acute leukemias Chronic leukemias Myelofibrosis Myelodysplastic syndrome Hairy cell leukemia Hodgkin lymphoma**	Typically, HLA-matched sibling or MUD
Haploidentical	A type of allogeneic transplant. Think "haplo" for "half match" for the patient	Acute leukemias Chronic leukemias Myelofibrosis Myelodysplastic syndrome Hairy cell leukemia Hodgkin lymphoma**	Typically, parents, children, siblings

Abbreviations: HLA, human leukocyte antigen; MUD, matched unrelated donor.
Definitions obtained from the National Cancer Institute (NCI) dictionary of cancer terms [10] and Kimmel Cancer Center.[11]
* Hodgkin lymphoma with no advancement to bone marrow.
** Hodgkin lymphoma relapse following autologous HCT or advancement to bone marrow.

Conditioning is a phase during the pre-HCT period where high-dose chemotherapy—and sometimes total body irradiation—are administered to the patient to suppress the rapidly dividing, malignant blood cells before donor stem cell transfusion.[12] The prescribed chemotherapy regimen for patients with HCT is generally specific to the classifications of HCT indicated, malignancy, and if the patient will receive full- or reduced-intensity conditioning chemotherapy. Typically, there is a period of "rest day(s)" between conditioning chemotherapy and stem cell transfusion. The goals of conditioning chemotherapy prior to HCT are to achieve adequate immunosuppression to prevent graft rejection.[13] See Table 2 for selected conditioning regimens for allogeneic HCT. In TCT settings, days are usually counted in reference to the day of transplant, or Day 0. The sample conditioning regimens in Table 2 will be administered during days -7 to -1.

Older adults may not be physiologically able to receive full-intensity conditioning chemotherapy regimens because of the increased risk of toxicities.[14–17] Full-intensity therapy (eg, myeloablative) may be indicated if reduced-intensity conditioning will not produce adequate myelosuppression for treatment.[17] The interprofessional TCT team will carefully consider the risks and benefits of full-versus reduced-intensity conditioning chemotherapy before HCT care planning, and will include the patient and caregiver in shared decision-making about the appropriate course of action.[18]

Frailty and Chemotherapy in Older Adults

High-dose chemotherapy may increase the risk of frailty in certain circumstances.[19] Frailty is defined as the physiologic changes associated with aging, characterized by patient-reported fatigue, low physical activity, slow walking speed, and unintentional weight loss, and may pose an increased risk for HCT-related mortality.[19,20] There is no single presentation of frailty; two frail patients may present with a range of phenotypes, including weight loss/cachexia, slow gait speed, poor grip strength, and self-reported exhaustion.[20,21]

In patients with leukemia who are frail, toxicities from chemotherapy may produce more adverse events of treatment than non-frail patients. Frail patients may not tolerate chemotherapy effectively because of age-related renal and hepatic impairment and drug-to-drug interactions.[22] To identify patients who have frailty or may be at risk of developing frailty during the course of conditioning chemotherapy, nurses can consult with the interprofessional TCT team regarding a battery of validated and comprehensive geriatric assessments. Geriatric assessments are focused evaluations of physical performance, frailty, comorbidity, polypharmacy, cognitive performance, and nutritional status that help understand the physiologic effects of aging in older adults prior to HCT.[22] Several geriatric assessments can be performed by nurses, including the Geriatric Assessment in Hematology

Table 2
Selected conditioning chemotherapy and TBI regimens prior to HCT for treatment of leukemia.

Regimen	Drugs	Days of cycle relative to day of transplant (Day 0)	Myeloid or lymphoid leukemia
Flu-Bu-Cy (low dose)	Fludarabine, busulfan, cyclophosphamide	Flu -7 to -2 Bu -7 to -4 Cy -3 to -2	Myeloid
Flu-Mel-Thio	Fludarabine, melphalan, thiotepa	Thio -7 Mel -6 Flu -5 to -2	Myeloid or lymphoid
Thio-Flu-Bu	Thiotepa, fludarabine, busulfan	Thio -6 to -5 Flu -4 to -2 Bu -4 to -2	Myeloid
Flu-Cy-TBI	Fludarabine-cyclophosphamide-TBI	Flu -6 to -2 Cy-6 to -5 TBI -1	Lymphoid
Flu-TBI (reduced intensity)	Fludarabine-TBI	Flu -4 to -2 TBI -1	Myeloid

Abbreviation: TBI, total body irradiation; HCT, hematopoietic cell transplant.
Selected regimens from Gyurkocza and Sandmaier.[13]
Cycle days from Shabbir-Moosajee et al,[14] and Jethava et al.[15]

scale, Geriatric 8, and Clinical Frailty scale.[14,23,24] In addition, there are scales used by TCT teams to assess comorbidity in adult patients who are not specific to older age groups, such as the HCT-specific comorbidity index.[25] Research has suggested that it is feasible to routinely incorporate geriatric assessment before cancer treatment begins at inpatient and outpatient settings.[26] Assessment findings may uncover latent problems that can be managed to avert or reduce treatment-associated toxicity.

Nurses have an important role in assessing the older patients' tolerance of chemotherapy before HCT. This includes performing a comprehensive physical assessment and asking relevant questions about the patient's physical functioning, nutritional status, fall risk, and cognitive performance. Because older patients' physical function can be labile during the HCT trajectory, the nurses' assessments will be a crucial component of HCT care planning. Assess whether the patient's condition has changed based on the bedside report from the previous nurse. It is also recommended that nursing staff attend the interprofessional TCT care team's rounds and communicates the status of the patient's condition frequently, and as their condition changes.[18,27]

Chemotherapy Administration and Monitoring in HCT

Central venous access

Patients undergoing HCT will have a central venous catheter (CVC) inserted before commencing treatment. The CVC is needed to safely deliver high volumes of blood products and conditioning chemotherapy but also provides quick access for blood draws and laboratory tests. Typically, patients will receive a tunneled catheter (eg, Hickman catheters) or peripherally inserted central catheter (PICC). Chest ports are not typically used during the pre-transplant phase of HCT.

Because patients will undergo a prolonged period of immunosuppression and myelosuppression during HCT, the risk for a central line-associated bloodstream infection (CLABSI) is notably high. Approximately 9% of patients receiving allogeneic HCT will develop a CLABSI.[28,29] Evidence suggests that the most common organism causing a CLABSI is *Staphylococcus epidermidis*, a bacterium naturally found on the skin.[29] Nursing interventions to prevent CLABSI include performing a sterile dressing change if found soiled, wet, or if dried blood is at the insertion site; educating the patient on the use of antimicrobial soap (eg, chlorhexidine) during daily bathing; flushing unused lumens of the CVC with heparin or saline solution, and always performing appropriate hand hygiene.[28]

It is important to have specific plans of care or guidelines for CLABSI prevention in place. It is also necessary to involve the patient's family caregivers in central line hygiene education because the CVC may remain in place following discharge after allogeneic HCT.

Pharmacokinetics

The nurse also plays a pivotal role in assessing the pharmacokinetics of chemotherapy. Pharmacokinetics is defined as the study of absorption, distribution, metabolism, and excretion of drugs by the body.[30] The metabolism of many chemotherapy and non-chemotherapy drugs must be monitored diligently because the therapeutic margins are narrow and potentially dose-limiting. Some conditioning chemotherapy drugs for allogeneic HCT, such as busulfan, require close monitoring and multiple blood draws after the first dose and up to 12 to 16 hours following infusion.[11,31] Examples of other drugs that require diligent serum monitoring and patient blood draws two to three times per week are methotrexate, tacrolimus, and vancomycin, among others.[31]

Chemotherapy safety

In addition to assessing the pharmacokinetics of chemotherapy, nurses are responsible for safe handling practices during the administration of chemotherapy drugs. The inherent hazardous, toxic nature of chemotherapy drugs puts nurses and other health care workers at risk of unintended exposure.[32] Given that many chemotherapy drugs treat cancer by disrupting the structure and replication of DNA in malignant and non-malignant cancer cells, even small exposures to chemotherapy drugs (ie, a few drops of fluid) are harmful to health workers.[32,33] For example, one study found that nurses and pharmacy workers with occupational exposures to chemotherapy were observed to have 50% higher DNA strand breaks than healthy controls.[34] Additionally, many myeloablative chemotherapy drugs administered in HCT settings are known carcinogens, including busulfan, cyclophosphamide, melphalan, and thiotepa.[32] However, there is no conclusive evidence that nurses with occupational chemotherapy exposures are more likely to develop cancer than nurses with no occupational exposures. Regardless, exposure prevention is essential.

The National Institute for Occupational Health and Safety recommends that personal protective equipment must be worn during the preparation, administration, and disposal of chemotherapy drugs and materials.[35] We suggest assessing your clinical workplace's practice guidelines and policies for more details.

Transplant Day Considerations

ABO incompatibility in allogeneic HCT

A few days before transplant nurses should communicate with the interprofessional TCT team and to confirm if ABO incompatibility is known from the HLA-matched donor. ABO incompatibility refers to the presence of antibodies, called *isoagglutinins*, in the recipient's and/or donor's A and/or B red blood cell antigens.[36–38] The severity of ABO incompatibility is classified as either major, minor, or bidirectional, depending on where the isoagglutinins are present. One study estimates that approximately 50% of unrelated donor transplants and 30% of related donor transplants demonstrate some level of ABO incompatibility.[36] Therefore, it is likely that nurses will likely care for a patient undergoing allogeneic HCT with ABO incompatibility throughout their career.

Symptoms and adverse effects of ABO incompatibility include acute and delayed hemolysis, non-hemolytic transfusion reaction, and delayed engraftment.[36,38] If a patient is known to have ABO incompatibility during HCT, it is important to perform assessments and interventions for acute or delayed transfusion reaction symptoms, including fever, chills, shortness of breath, back/flank pain, rigors, and fatigue.[39] Nurses should communicate with the interprofessional TCT team early and frequently to optimize patient safety and mitigate the worsening of issues.

Transplant day

The day of allogeneic HCT—often referred to as transplant Day 0—is a much-anticipated moment for the patient and their family/support system. The patient will finally receive their related or unrelated stem cells to treat their hematologic cancer. The infusion of bone marrow or peripheral blood stem cells through the CVC is very similar to a blood product infusion; the bag and tubing apparatus will vary if bone marrow or peripheral blood stem cells.[9] The nurse will assemble and prime the transplant tubing, and place emergency equipment (eg, anaphylaxis kit, suction) at the bedside in the event of a transfusion reaction.[9]

The nurse will need to assess the scheduled time of transplant to coordinate and plan ahead for their assignment's workload. Unrelated donor stem cells may be transported by airplane from anywhere in the world; however, delivery time is usually written in the pre-HCT documentation. Related donor stem cells will be collected very close to Day 0, often the same morning or a couple of days prior. The nurse should also assess when the patient's last dose of chemotherapy was administered. Many conditioning regimens include at least one rest day prior to HCT. If chemotherapy is administered too soon before transplant the efficacy of treatment may be reduced because the drug is still being metabolized by the renal or hepatic systems.[40] This assessment is more crucial for autologous HCT but is still good practice for nurses administering allogeneic HCT.

Although Day 0 is highly anticipated, many patients report that the transplant process is "anti-climactic" because the infusion process seems identical to other blood product infusions. Patients may process transplant differently—with excitement or anxiety—nurses can support the patient by allowing them to process this change.

Post-HCT Considerations

Supportive care for symptoms

Once the HCT is performed, the nurses' focus of care shifts to the management of chemotherapy toxicities and psychosocial challenges. In the following section, we focus primarily on important symptom management considerations for nurses. Please refer to the other chapters in this issue of *Seminars in Oncology Nursing* for psychosocial considerations during HCT.

Certain symptoms or toxicities of chemotherapy are expected to occur after receiving myeloablative or myelosuppressing chemotherapy.[41] Symptoms may intensify around the period of profound cytopenia, called *nadir*, when the neutrophil, red blood cell, and platelet counts are the lowest.[42,43] Table 3 provides a list of common symptoms and supportive care needs to assess for and intervene. Irwin and Johnson provide an excellent resource of symptom management.[44]

Between nadir and engraftment, nurses are responsible for assessing fatigue, shortness of breath, bleeding, unsteady gait, and the overall patient condition in relation to the patient's hemoglobin and platelet counts. It is important for the nurse to determine the need for blood products (ie, packed red blood cells, platelets), fall precautions, careful oral hygiene, and protective precautions as medically indicated. The nurse will typically administer granulocyte colony stimulating factor drugs by subcutaneous injection to shorten the time from neutropenia to engraftment, and reduce the risk of neutropenic fevers.[45]

Patients with mucositis will need adequate pain management with oral or IV analgesics to successfully maintain proper nutrition. Nurses can work with a registered dietitian or other dietary experts in the TCT team to recommend non-irritating foods and fluids in this circumstance. Oral intake and daily weight recordings should be assessed with each patient encounter. For at-risk patients, a strict multi-day caloric intake diary might be ordered. For patients with severe mucositis, stomatitis, and/or esophagitis, the physician will place orders for total parenteral nutrition with or without lipids for nutritional needs. Additional considerations for nursing care of a patient requiring total parenteral nutrition with lipids include frequent assessment of blood glucose levels, IV drug compatibility and access, daily tubing and CVC cap changes, and increased risk for CLABSI.[46]

GVHD

GVHD is an anticipated complication of allogeneic HCT that occurs in approximately 40% to 60% of HCT recipients.[47] GVHD presents in both acute and chronic etiologies and ranges in severity.[48] Among HCT recipients, GVHD is associated with a 50% mortality rate and is one of the top three causes of death for HCT recipients.[49,50] There are multiple evidence-based risk factors associated with the risk of GVHD, including advanced age, donor-recipient HLA-mismatch, the intensity of conditioning chemotherapy, and recipient presence of cytomegalovirus.[48,51]

Acute GVHD occurs when HCT donor-derived T lymphocytes produce a cytotoxic response against the host's (ie, patient's) cells.[52] Acute GVHD occurs within the first 100 days after HCT and leads to cellular damage, generally in the gastrointestinal tract, liver, and skin. Whereas chronic GVHD occurs beyond 100 days post-HCT and may present in HCT survivors up to 2 to 3 years, on average.[53] The pathophysiology of chronic GVHD is less understood than in acute GVHD. However, evidence suggests that co-occurring effects from the patient's new T lymphocytes and donor-derived T lymphocytes may influence chronic GVHD.[54] Evidence shows chronic GVHD most commonly occurs in the skin, liver, and mouth, but may occur in the lungs, vagina, and other organs.[55] The most frequently observed acute and chronic GVHD organ involvement and estimated incidence statistics are provided in Table 4.[56–58] If acute or chronic GVHD is suspected, the TCT team will arrange for medical testing to confirm a diagnosis (eg, endoscopy, skin biopsy, serum bilirubin tests).

Nurses have a significant role in assessing the onset of GVHD, delivering supportive care, and educating patients and caregivers. In the presence of acute and chronic GVHD, the nurse's role within the interprofessional TCT team includes the assessment and grading of acute and chronic GVHD and providing supportive care. For example, in the presence of acute GVHD of the gastrointestinal tract, nursing assessments and interventions will encompass strict and accurate measurement of stool output, identifying signs of hemorrhage, and assessing and managing abdominal pain.

The go-to therapies for acute and chronic GVHD are corticosteroids, often prescribed in high-dose regimens, to yield an immunosuppressing effect.[51] HCT recipients with chronic GVHD may be prescribed corticosteroids for up to 3 years post-HCT.[59] Adherence to corticosteroids is an essential teaching point for TCT nurses to educate patients with chronic GVHD. Missed doses of corticosteroids may lead to worsening of symptoms, and tapering to lower doses may occur over a 3- to 4-month period. In older adults, the symptoms associated with long-term corticosteroid use include hypertension, hyperglycemia, infections, euphoria, osteoporosis, and easy bruising.[51] Anti-infective prophylaxis is common during prolonged durations of high-dose corticosteroid use.[51] Pharmacologic interventions to prevent GVHD following allogeneic HCT include low-dose methotrexate, tacrolimus, and mycophenolate among others.

Extracorporeal photopheresis

One advanced intervention for patients with severe GVHD is extracorporeal photopheresis (ECP).[60] During ECP, patients will have blood collected through apheresis, followed by separation of a small percentage of white blood cells (3% to 5%) and treatment with a photosensitizing medication (eg, methoxsalen).[60] Next, the ECP machine

Table 3
Common symptoms and supportive care needs during HCT nadir and engraftment.

- Fatigue
- Nausea
- Vomiting
- Diarrhea
- Neutropenic fever
- Pain
- Constipation
- Mucositis (and/or esophagitis, stomatitis)
- Rash (and/or engraftment syndrome)
- Decreased appetite
- Changes with taste
- Insomnia
- Difficulty with concentration and memory (ie, chemo brain)
- Anxiety
- Depressive symptoms

Table 4
Common acute and chronic GVHD clusters and incidence estimate percentages.

Acute GVHD (0–100 Days post-HCT)		Chronic GVHD (> 100 days post-HCT)	
Involvement	Incidence (%)	Involvement	Incidence (%)
GI (gut)	54%–63%	Skin	65%–80%
Skin	15%–35%	Liver	40%–73%
Liver	1%–8%	Eye	18%–47%

Abbreviations: GI, gastrointestinal; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant.
Incidence statistics retrieved from: McDonald,[56] Jacobsohn and Vogelsang,[57] and Chao.[58]

uses ultraviolet A radiation to activate the medication and then re-infuses the treated white blood cells to the patient.[60] The methoxsalen-treated white blood cells will produce an immune response that will mitigate the effects of chronic GVHD.[60] The frequency and duration of ECP for GVHD treatment varies, and a clinical benefit may not be assessed until weeks into the therapy.

ECP is not delivered at all TCT settings. Education topics for nurses to deliver to patients undergoing ECP include infection prevention (for the CVC catheter), care of the CVC site, and adequate caloric intake. For patients undergoing ECP in the hospital, nurses' may be responsible for a number of assessments and tasks, including administering packed red blood cells or IV electrolytes before treatment, and heparin-locking the CVC.[61]

Conclusion

HCT is an effective but high-risk and potentially curative therapy for older adults with leukemia. There are myriad of clinical complications and nursing considerations during HCT, including chemotherapy administration, supportive care for symptom management, infection prevention, and assessment of acute and chronic GVHD. Additional topics for nurses to consider for the older adult undergoing HCT include psychosocial support for the patient and caregiver, palliative and end-of-life care, nutritional support during the post-HCT phase, and the emergence of novel therapies to treat hematologic malignancies, such as chimeric antigen receptor T-cell therapy. Additional literature on these topics can be found in the other chapters in this issue of *Seminars in Oncology Nursing*. Nurses who are well-versed and competent in the broad roles involved before, during, and after an allogeneic HCT will optimally be able to meet the needs of patients' and their caregivers.

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