High-Dose Chemotherapy With Autologous Stem Cell Rescue in the Outpatient Setting

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Intensive outpatient care is rapidly becoming the primary mode of care for selected patients undergoing high-dose chemotherapy with autologous peripheral blood stem cell (PBSC) transplantation. Although the traditional inpatient model of care may still be necessary for high-risk patients, published data suggest that outpatient care is safe and feasible during or after administration of high-dose chemotherapy and autologous PBSC transplant. Blood and marrow transplant (BMT) centers have developed programs to provide more outpatient care under three basic models: an early discharge model, a delayed admission model, and a comprehensive, or total, outpatient model. This review will describe these models of care and address the elements necessary for the development of an outpatient BMT program, including patient selection, staff development, and patient and caregiver education. Available supportive care strategies to facilitate outpatient care will also be highlighted.

Introduction

Advances in the field of blood and marrow transplantation (BMT) leading to decreased morbidity and mortality have facilitated a shift in care of the transplant patient from the hospital to the outpatient clinic. One major factor that has facilitated this shift is the increased use of peripheral blood-derived stem cells (PBSCs) instead of bone marrow-derived stem cells as autologous rescue following administration of high-dose chemotherapy.[1]

The use of PBSCs is associated with shorter periods of neutropenia and thrombocytopenia, as well as potentially less severe regimen-related toxicities.[2-4] In addition, improvements in supportive care strategies, including antibiotic algorithms for prophylaxis and treatment, antiemetic regimens, and transfusion protocols, have allowed patients to be cared for safely in the outpatient setting. The potential advantages of outpatient care for BMT patients include improved patient satisfaction and quality of life by allowing them to remain in their home environment or in a nearby hotel. In addition, the elimination of a prolonged hospital stay may potentially decrease the convalescent period by keeping the patient more active and responsible during the transplant process.[5] Published data in cancer patients support these potential advantages of outpatient care during BMT.[6,7] Despite the potential impact of outpatient care on quality of life, thus far, the primary end points evaluated have been safety, feasibility, and pharmacoeconomics.[8,9] Numerous studies have documented the safety and feasibility of outpatient care during or after administration of high-dose chemotherapy with autologous PBSC rescue.[10-14] In terms of pharmacoeconomics, autologous BMT has traditionally been an expensive procedure, with historical costs exceeding $100,000 per patient. Attempts to decrease this cost have been fueled by the general pressure to decrease health care costs and the increasing use of global-fee contracts for BMT, in which the provider assumes the financial risk for all BMT services.[15,16] Establishment of an outpatient component of care early in the BMT process requires prudent patient selection, intensive planning and education, trained staff, and appropriately equipped facilities. This review will address the logistic requirements and published outcomes for various outpatient BMT care models.

Models of Outpatient Care

Three models of outpatient care have been described in the literature and are represented schematically in Figure 1.

Early Discharge Model
The first outpatient care model described, the early discharge model, was implemented by Peters et
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al at Duke University.[10] In this program, high-dose chemotherapy is administered on the hospital BMT unit. After the completion of high-dose chemotherapy and stabilization of gastrointestinal toxicities, patients are discharged to the outpatient BMT clinic and followed on a daily basis. During this period of intensive outpatient visits, patients are readmitted to the inpatient BMT unit only if they develop such complications as neutropenic fever, refractory gastrointestinal toxicities, or other clinical scenarios that cannot be managed in the outpatient setting.[10] By implementing this approach, Peters et al reported a reduction in BMT-associated hospital stays from 24.5 to 7 days.

**Delayed Admission Model**
Another model described less extensively in the literature, but used in numerous autologous transplant centers, is the delayed admission model of Weaver et al.[11] In this model, high-dose chemotherapy is administered in the outpatient setting, and patients are then admitted to the hospital for supportive care management. Although the delayed admission approach can decrease the duration of hospitalization as compared to the traditional inpatient model, patients generally require 2 weeks of hospitalization during the supportive care period.[11] For example, although the delayed admission model is referred to as an outpatient BMT program, Weaver et al reported that 96% of 80 patients with lymphoma undergoing autologous transplantation required hospitalization for a median of 14 days.[11]

**Total Outpatient Model**
Recently, a more extensive approach to outpatient care has been described, which can be defined as a total, or comprehensive, outpatient model.[12-14] In this model, both high-dose chemotherapy administration and supportive care management are conducted in the outpatient setting, with patients hospitalized for complications that cannot be managed in the clinic or at home. Of the three outpatient models, the total outpatient approach is associated with the shortest duration of hospitalization, but it is the most labor intensive for the outpatient BMT clinic. The comprehensive outpatient care model requires extensive coordination and implementation of resources, often including the establishment of specialty designated outpatient clinics and home health care programs.

**Resources Needed for Outpatient Care**
Providing care to the BMT patient in the outpatient setting requires the availability and establishment of numerous facility and staff resources. The extent to which certain resources are needed depends on the established outpatient care model. Essential resources for every model include a designated outpatient and inpatient care facility. Most outpatient programs have an equipped outpatient facility that operates during regular business or extended hours. The mechanisms used to provide after-hours or weekend care vary among centers, however. Options implemented include extended clinic hours or direct admission to the hospital for any complications occurring after hours.[10] Another option that may minimize hospitalization is the establishment of a hospital-based outpatient treatment room for weekend and emergency visits.[14] Provision of after-hours care may also depend on the level of home health care nursing and infusion services available.

**Specialized Staff**
The availability of dedicated, specialized staff is crucial to the success of an outpatient BMT program. Essential staff members include inpatient and outpatient BMT-trained nurses, pharmacy services specializing in high-dose therapy, laboratory and blood-banking support, medical and surgical consultants, and hematopoietic cell therapy support services. In addition to these essential staff members, which are common to all outpatient models, other personnel have been added or adapted within various centers based on need and available resources. For example, the level of home health care involvement among outpatient BMT programs ranges from minimal to extensive. The model of Peters et al provides only minimal home health care support and, at one point, used home health care professionals primarily for ambulatory pump needs.[10]

In contrast, the model of Geller et al integrates BMT-designated home health care nursing staff into the daily care of the patient.[14] In this model, the BMT home health care staff consists of inpatient BMT nurses who rotate weekly. During the home health care week, their only responsibility is to answer telephone calls, make home visits for initial assessments and follow-up care, and provide primary nursing care to patients seen in the weekend outpatient BMT clinic. Complete integration of home health care into the outpatient BMT program can expand the comprehensiveness of the program and help eliminate the need for short hospital stays to initiate
intravenous antibiotics for a first neutropenic febrile episode.[14] However, in other models with less home health care involvement or prolonged clinic hours, patients may be admitted to the hospital for evaluation and initiation of intravenous antibiotics.[10,11]

### Outpatient BMT Candidate Selection and Preparation

Before determining the appropriateness of outpatient care, the BMT candidate first undergoes the routine pre-BMT evaluation to determine eligibility. This evaluation includes an assessment of clinical eligibility based on disease restaging, organ function, and performance status, as well as a psychosocial assessment and investigation of insurance coverage.

#### Patient Selection Criteria for Outpatient Care

Once candidacy for BMT is confirmed, or as this process is ongoing, patients are screened to determine candidacy for outpatient care (Table 1). Despite the increasing use of outpatient care, available data on specific criteria for outpatient care are limited and vary among transplant centers, based on institutional protocols and resources. In general, most centers agree that in order to safely care for the patient in the outpatient setting, patients must have housing within close proximity to the transplant center (ie, 30 minutes’ driving distance) and have one or more caregivers available to assist in the care of the patient outside the clinic setting.[10,12-14]

For patients who live more than 30 minutes’ driving distance from the transplant center, most programs arrange for local housing in a nearby apartment or hotel. One example of lodging facilities used to facilitate outpatient BMT is the Hope Village, an on-site, temporary housing project located within 200 yards of the City of Hope National Medical Center.[17] The Hope Village has small houses with individual suites equipped with emergency phone and activation devices, as well as a speaker system to designated security or BMT program personnel.[17]

The Duke program uses a hotel located next to their outpatient clinic for temporary lodging during outpatient BMT care. The hotel has designated, discounted rooms for BMT patients and provides special housekeeping services to minimize the risk of infection.[10] Such temporary lodging is often reimbursed by the third-party payor or is covered under global rate agreements.[12,15] Along with adequate lodging, reliable transportation for daily and emergency visits is an important criterion to consider when screening candidates for outpatient care.

#### Psychosocial Assessment—

Selected centers have expanded their criteria for outpatient BMT care to include an extensive psychosocial assessment by a social worker or psychologist familiar with the BMT process.[5,14] This assessment attempts to establish the coping skills and compliance of the patient and designated caregivers, as well as identify obstacles, such as poor family dynamics or unavailable resources, that could hinder the success of outpatient care.

#### Home Assessment Visit—

The model of Geller et al incorporates the use of a home assessment visit prior to outpatient BMT care to help determine candidacy for outpatient care.[14] A BMT home health nurse visits the patient’s private home or designated lodging and conducts an inspection for risk of infection and other health hazards. During this visit, the BMT home health nurse also educates the patient and caregivers on how to prepare themselves and their environment for the outpatient treatment process. Examples include designating one bathroom for the patient and cleaning this facility daily, removing living plants from the area where the patient will spend time, limiting contact with small children during the outpatient process, and designating a separate caregiver for any children.

#### Assessment and Education of Caregiver(s)—

Another aspect that is important for determining candidacy for outpatient care is the competency and commitment of the caregiver. The availability of responsible caregivers once high-dose chemotherapy is initiated is vital to the success of outpatient care. Limited information is available on established criteria or certification systems to ensure the competency and commitment of the caregiver, although a recently published series addressing family caregivers and the marrow transplantation experience provides useful information.[18-20]

Other experts have also emphasized the importance of selecting appropriate caregivers and developing educational and resource strategies for them. Stetz et al identified essential informational and resource needs of caregivers of patients undergoing BMT.[20] Educational materials should target the following areas: preparation for and management of patient care, the ability to face challenges, development of supportive strategies, and recognition of unanticipated rewards.

In addition, Stetz et al emphasized the importance of providing the caregiver with written, up-to-date information with specific instructions. The Fred Hutchinson Cancer Research Center has developed...
“The Caregiver Program,” which involves a series of classes, including an orientation session and separate classes on caregiving, use of an ambulatory pump, and assistance with patient recovery.[20]

**Barriers to Outpatient Care**—Regardless of the level of preparation of the BMT program, barriers to outpatient care exist and warrant consideration during patient selection. Meisenberg et al reported that 18% of eligible patients did not participate in the subtotal or total outpatient BMT program due to lack of a caregiver (N = 8), patient refusal because of a lack of comfort with outpatient treatment (N = 4), or evidence of a medical condition that required inpatient care (N = 4).[12]

According to Sharma et al, of the first 75 consecutive patients offered care in their outpatient transplant program, only 18 (24%) underwent transplantation in the outpatient setting.[21] Of the 57 patients transplanted in the traditional inpatient setting, the following obstacles precluded outpatient care: psychological factors, including severe anxiety or compliance concerns (29%); patient refusal (13%); financial limitations, including a lack of insurance coverage (12%); lack of a caregiver (12%); and complex medical history with underlying comorbid illnesses (9%).

**Facilitating Medical Management in the Outpatient Setting**

Most of the published literature has addressed specific supportive care issues related to medical management early in the BMT process, based on the assumption that patients are hospitalized during this time frame. The increasing use of outpatient care during this period has necessitated modifications to the management of the BMT patient. Areas requiring special attention include delivery of high-dose chemotherapy, prevention and treatment of infection, prevention and treatment of gastrointestinal complications, pain management, fluid and electrolyte support, and central venous catheter care.

**PBSC Mobilization Regimens**

Strategies for the mobilization of PBSCs vary among centers, as do the care plans for patients during PBSC mobilization. The most common mobilization strategies involve the use of colony-stimulating factors, with or without myelosuppressive chemotherapy.[22]

For regimens employing colony-stimulating factors alone, filgrastim (Neupogen) or sargramostim (Leukine) are administered subcutaneously daily, with leukapheresis beginning on the fourth or fifth day of colony-stimulating factor therapy.[23,24] This regimen rarely requires hospitalization, and most patients safely administer their own colony-stimulating factor injections. In general, this regimen involves one clinic visit to initiate colony-stimulating factor therapy and provide education on self-administration of subcutaneous injections. Leukapheresis is then initiated and continued on an outpatient basis in BMT-designated facilities.

Combination chemotherapy and colony-stimulating factor mobilization regimens typically incorporate high-dose cyclophosphamide (Cytoxan, Neosar), with or without additional myelosuppressive drugs, followed by daily subcutaneous administration of colony-stimulating factors through the completion of leukapheresis.[25-27] Although this regimen may enhance progenitor cell collection yields, it is more labor intensive and causes a 7- to 10-day period of neutropenia. The patient may require hospitalization to manage such complications as neutropenic fever.[25] Medical management strategies and criteria for outpatient care during the period of neutropenia are similar to those following administration of high-dose chemotherapy regimens.

**High-Dose Chemotherapy Regimens**

Various high-dose chemotherapy regimens have been developed and are well established in the autologous BMT setting.[28-32] Specifics of these regimens may limit their applicability for outpatient administration, however. Such specifics include the route, frequency, and ease of administration of chemotherapy and the need for supportive care medications during chemotherapy administration. As mentioned previously, the level of available resources and the patient care model may also affect the feasibility of outpatient high-dose chemotherapy.

Table 2 lists examples of regimens that are feasible for outpatient administration, along with schematics of administration for two regimens.[12,14,33,34] In some cases, modifications to the originally published regimens have been made to facilitate outpatient delivery. For example, a modification in the high-dose chemotherapy STAMP V regimen facilitates its outpatient delivery. This regimen incorporates total regimen doses of 6,000 mg/m² of cyclophosphamide, 500 mg/m² of thiotepa (Thioplex), and 800 mg/m² of carboplatin (Paraplatin).[31] The initial protocol used continuous 24-hour infusions of these drugs over 4 days.[31]

Although continuous infusions of certain regimens, such as VAD (vincristine, Adriamycin, and
dexamethasone), have been administered safely in the outpatient setting, administration of the STAMP V regimen in such a manner would require the use of multiple ambulatory pumps, since each drug must be delivered via a separate infusion lumen.

In an attempt to simplify this regimen, Weaver et al described a modified STAMP V regimen that delivers the same total regimen dose of each drug divided over 3 days as 1-hour infusions on each day.[33] Since these drugs are not cell-cycle-specific, continuous infusions should not enhance their efficacy. Based on these and other pharmacokinetic and pharmacodynamic properties of the drugs, bolus administration should not alter their efficacy. Indeed, a recent study using this modified STAMP V regimen in metastatic breast cancer patients reported results similar to those published using the original continuous-infusion STAMP V regimen.[35]

**Antiemetic Regimens**

Data on the management and prevention of nausea and vomiting following high-dose chemotherapy and BMT continue to be limited. Published data on prophylactic antiemetic regimens administered with high-dose chemotherapy given in the inpatient setting describe the use of intravenous granisetron (Kytril) or ondansetron (Zofran). Use of either of these serotonin antagonists resulted in complete or near-complete prevention of emesis in 76% to 87% of patients on the first day of chemotherapy and in 51% to 52% on subsequent days.[36-38]

One limiting factor reported in a pilot trial evaluating the feasibility of outpatient care during BMT in breast cancer patients receiving the STAMP V regimen is a prolonged need for intravenous antiemetics to manage nausea and vomiting.[39] In this pilot trial, Miyahera et al reported that 40% of patients required a median of 7 days of intravenous antiemetics, despite initial efforts to prevent nausea and vomiting with oral serotonin antagonists, lorazepam, and dopaminergic pathway medications.

Conversely, Frakes et al achieved successful control of emesis in patients undergoing high-dose chemotherapy plus autologous PBSC transplantation with an all-oral anti-emetic regimen comprised of granisetron, prochlorperazine, and dexamethasone.[40] With this regimen, the authors reported a 53% complete response rate and 75% complete or major response rate for emesis during all 5 treatment days.

Although the data from Frakes et al are encouraging, previous data and experience have prompted many clinicians performing outpatient BMT care to develop and implement intravenous antiemetic regimens that can be safely and effectively administered in the outpatient setting. Although little descriptive data have been published, a variety of antiemetic regimens have been used to facilitate delivery and recovery from high-dose chemotherapy in the outpatient setting (Table 3).[14,15,38,41]

A more descriptive report was recently presented outlining the use of once-daily doses of intravenous serotonin antagonists on days of high-dose chemotherapy combined with continuous intravenous infusions of Benadryl, Ativan, and dexamethasone, also called the BAD pump, to facilitate delivery of high-dose chemotherapy in the outpatient setting (Figure 2).[42]

**Antibiotic Algorithms**

Over the past few years, progress has been made in both the treatment and prevention of infection in BMT patients. Until recently, however, antibiotic algorithms, like other supportive care strategies, were designed based on the assumption that the patient would be hospitalized for the BMT procedure. More recently, however, strategies to prevent and treat infection have been modified to accommodate more outpatient care.[12,43-45] More importantly, these outpatient-based prophylactic regimens have been safe, effective, and associated with similar rates of infections as traditional inpatient antibiotic algorithms regimens (Table 4).

**Early Outpatient Regimen—**

Gilbert et al described one of the first outpatient-based anti-infective strategies for the prevention of infection in BMT patients.[43] This regimen incorporated preventive and empiric approaches to managing infection during neutropenia, both of which were conducive to outpatient administration. For prevention of infection, two oral prophylactic antimicrobials, ciprofloxacin (Cipro) and rifampin (Rifadin, Rimactane), were initiated soon after the completion of high-dose chemotherapy. Empiric, once-daily intravenous antibiotics, vancomycin and tobramycin, were added for neutropenic fever and continued until neutropenia resolved.

The incidence of neutropenic fever was reduced from 98% in a historical control group receiving no prophylaxis to 57% in patients receiving ciprofloxacin and rifampin. Bacteremia developed in none of the patients given the prophylactic regimen, as compared with 18% of the historical controls. The incidence of nephrotoxicity (defined as a serum creatinine level > 1.8 g/dL), was similarly low in both groups (< 10%). The incidence of ototoxicity also did not differ in the two groups, despite the higher peak levels of vancomycin and tobramycin achieved with once-daily dosing. Most importantly,
Regimens With Fewer Oral Drugs—Although effective, outpatient antibiotic regimens can be expensive and require the patient to tolerate multiple oral medications daily. As most patients experience some nausea and mucositis during the period requiring oral antibiotics, attempts to limit the number of oral medications needed are under investigation.

In a recent pilot trial, single-agent antibiotic prophylaxis with trovafloxacin (Trovan) was compared to prophylaxis with a quinolone plus cephalaxin in patients undergoing HDC followed by autologous PBSC transplantation.[46] Although the sample size was small (N = 40), initial data suggested that trovafloxacin was as effective as the quinolone plus cephalaxin in preventing infection and limiting the number of days of intravenous antibiotics required. In addition, the trovafloxacin regimen reduced the daily number of pills from six to one and the daily cost of medications by 50%. However, despite these encouraging results, prophylactic use of trovafloxacin is discouraged due to recently recognized drug-associated liver complications.

Management of First Neutropenic Fever

Although the data suggest that infection can be managed safely in the outpatient setting during high-dose chemotherapy with autologous PBSC transplantation, the number of patients who require admission to the hospital at the onset of neutropenic fever may vary among sites, depending on the availability of resources. For example, in the initial Duke model, if the first neutropenic fever occurred after clinic hours, the patient was admitted to the hospital for initiation of empiric intravenous antibiotics. However, if the first neutropenic fever occurred during clinic hours, empiric intravenous antibiotics were initiated in the outpatient clinic and the patient was allowed to return to the hotel, if clinically stable.[10]

In the model of Geller et al, the need for hospitalization for the initiation of empiric intravenous antibiotics in cases of uncomplicated neutropenic fever was eliminated by incorporating the services of a designated BMT home health care staff.[14] In this model, patients received an oral prophylactic regimen of ciprofloxacin, cephalaxin, and fluconazole (Diflucan), with or without acyclovir or valacyclovir (Valtrex). At the time of initiation of high-dose chemotherapy, the patient was sent home with an antibiotic kit containing intravenous tobramycin and supplies necessary for administration by the home health care nurse.

If the first neutropenic fever occurred during clinic hours, empiric therapy with once-daily intravenous tobramycin was initiated in the clinic, and the patient was allowed to return home if clinically stable. If the first neutropenic fever occurred after clinic hours and the patient was clinically stable, the home health care nurse evaluated the patient in the home or local lodging, drew blood for cultures and performed other necessary tests, and then initiated the first dose of intravenous tobramycin in the home.

By incorporating the home health care team in the model of Geller et al, only 34% of patients required readmission to the hospital for any reason, as compared with 54% of patients in the Duke model.[10,14] None of the hospitalizations in the Geller et al model was for first neutropenic fever, as compared with 24% of the hospitalizations in the Duke model.[10,14]

Nonpharmacologic strategies may be important in preventing infection in the outpatient BMT setting, but these strategies have not been appropriately evaluated. Such nonpharmacologic strategies include adherence to a low-microbial diet during neutropenia and modification of the home environment to minimize the risk of infection. Modifications in the home environment include removal of live plants from the patient’s immediate vicinity, frequent cleaning of bathroom facilities with antibacterial cleaners, and minimization of contact with infants or small children. The success of nonpharmacologic strategies in decreasing the risk of infection is less tangible, but such strategies are considered important components of standard care in many programs and require extensive education of patients, caregivers, and staff.

Other Supportive Care Strategies

Development of supportive care strategies in addition to those designed to minimize infection, nausea, and vomiting is also essential to the success of an outpatient care approach during BMT. These supportive care strategies include pain management, prevention of hemorrhagic cystitis, fluid and electrolyte management, nutritional support, and care of central venous catheters, among others.[39,41,47-49] These aspects of supportive care have been accomplished safely in many outpatient BMT centers. However, should complications arise, limited published data describe how to successfully manage or prevent them in the outpatient setting.

Table 5 outlines some of these supportive care strategies. Three specific areas—fluid and electrolyte
management, nutritional support, and care of central venous catheters—warrant further discussion. **Management of Fluid and Electrolytes**—Because of the limited time available to evaluate patients in the clinic, it may be more difficult to monitor fluid volume and status. Approaches that help ensure safe fluid management in outpatient BMT patients include comprehensive fluid intake and output monitoring and recordkeeping by the patient and/or caregiver. Availability of this information for daily review can assist the team in making decisions about the need for intravenous hydration and/or diuresis. Administration of intravenous fluid overnight or continuously by ambulatory infusion pumps is also a safe, commonly used approach to maintaining adequate fluid volume and providing electrolyte replacement. **Nutritional Support**—Standards for the administration of parenteral or enteral nutrition in BMT patients undergoing outpatient care also vary among centers. One recent publication describes a clinical pathway for nutritional management of BMT patients under-going outpatient care.[48] Because of the decreased period of neutropenia and lower severity of mucositis with PBSC rescue, many centers are observing a decreased need for supplemental nutrition. A recent trial suggests that parenteral nutrition can be safely administered in the outpatient setting following BMT, but reports no clinical benefit over intravenous hydration in a group of malnourished BMT patients.[49] **Central venous catheter care** is another area that warrants special attention when BMT is carried out in the outpatient setting. Recent advances in catheter technology have introduced new multilumen catheters that are sufficient for infusion needs and blood drawing, as well as leukapheresis. New catheters, such as the Neostar catheter, or redesigned Hickman catheters avoid the need for placement of two central venous catheters and allow the use of one catheter for multiple purposes. These catheters remain in place for several weeks to months and require diligent care by the staff, patient, and caregivers to minimize infection, thrombosis, and other catheter-associated complications. Education of the patient and caregiver is essential to ensure appropriate catheter care and recognition of potential complications in the outpatient setting. **Criteria for Hospital Admission** Establishment of admission criteria for hospitalization is also essential to the success of outpatient BMT care. Criteria have been published by various centers and share common principles.[12-14] For example, the criteria proposed by Meisenberg et al and Geller et al require that patients be readmitted for such complications as uncontrolled nausea, vomiting, or diarrhea; hypotension that is unresponsive to fluid replacement; severe mucositis requiring continuous intravenous narcotics; the absence of a suitable caregiver; or other conditions, at the discretion of the attending physician.[12,14] These two programs do not require automatic admission for first neutropenic fever, but other programs may stipulate such admission, depending on available resources and supportive care strategies. Other criteria that often warrant readmission include gastrointestinal complications, persistent bleeding, fever associated with signs and symptoms of sepsis, dehydration, symptomatic arrhythmias, or other significant organ dysfunction. Although these medically based admission criteria must be followed to ensure the safe care of the patient, less tangible, but equally important, psychosocial-based admission criteria must also be followed. Psychosocial issues that warrant admission include recognition that the caregiver is unable to meet demands of the outpatient program or that the patient has become noncompliant with outpatient-based instructions. **Pharmacoeconomic Data** The impact of outpatient care on the field of BMT has been assessed primarily in historical control-based trials or descriptive reports, which have documented a decrease in BMT-associated costs or resources without compromises in patient safety or the efficacy of the procedure. The Duke program was the first to note a substantial reduction in the duration of hospitalization and charges related to the BMT procedure after implementation of their outpatient care approach. Over a 2-year period, 110 women with primary metastatic breast cancer undergoing high-dose chemotherapy with autologous PBSC or bone marrow transplantation were evaluated.[10] The first 18 women were hospitalized for the entire procedure but were discharged to a local hotel each night. This group served as the pilot group to test the feasibility of the outpatient approach and served as the control group for comparison. The remaining 92 women were managed under the early discharge and outpatient care approach. Using this approach, 95% of the women were discharged following high-dose chemotherapy administration. In terms of readmissions, approximately 30% of patients required prolonged hospital stays for a median of 11 days and 24% required shorter hospital stays, ranging from 1 to 4 days.
usually for evaluation of first neutropenic fever. Subsequently, Meisenberg et al published the results of a prospective study evaluating the feasibility of a total outpatient care approach for administration of high-dose chemotherapy with autologous PBSC transplantation and post-BMT care.[12] In this study, 113 patients underwent 165 cycles of high-dose chemotherapy with autologous PBSC transplantation for various malignancies. The first cohort of patients participated in a subtotal outpatient transplantation approach, in which patients were hospitalized for high-dose chemotherapy administration, then discharged for supportive care, and readmitted only for complications that could not be managed in the clinic. After it was determined that subtotal outpatient transplantation was safe, subsequent patients were given the option of a total outpatient transplantation approach, in which all high-dose chemotherapy and supportive care were administered in the outpatient setting. Of the 165 cycles of high-dose chemotherapy, 85% of the cycles were delivered using one of the outpatient care approaches. With both approaches, approximately 70% of patients never required readmission to the hospital and were successfully and safely managed in the outpatient setting. Among the 30% of patients who required readmission, the median duration of hospitalization was 7 days for those who underwent total outpatient transplantation and 10 days for those who received subtotal outpatient transplantation. Other investigators have also noted a substantial reduction in overall duration of hospitalization for patients undergoing high-dose chemotherapy with autologous PBSC transplantation in the outpatient setting, as compared with patients requiring the same treatment in the traditional inpatient setting due to medical or psychosocial reasons.[13,14,16,50] Of note, engraftment rates, transfusion requirements, duration of intravenous antibiotic therapy, and rates of documented bacteremia were similar between the inpatient and outpatient transplant groups (Table 6).

**Overall Costs and Charges**

The reduction in resources achieved with outpatient care of BMT patients can result in substantial decreases in the overall costs and charges associated with high-dose chemotherapy and autologous PSPC rescue. In the Duke program, the average charge for the high-dose chemotherapy procedure decreased from $90,000 to $60,000 for adjuvant treatment of high-risk stage II-III breast cancer and from $115,000 to $90,000 for treatment of metastatic breast cancer.[15] Similarly, Meisenberg et al recently reported a 25% reduction in the overall cost of care in the total outpatient BMT program, as compared with traditional inpatient care.[51] The University of Nebraska BMT program also realized decreases in transplant associated costs, morbidity, and mortality over a 5-year period. Variables that contributed to these reductions included an increased use of PBSCs and a shift from inpatient to outpatient care during the transplant procedure.[34,52]

It is difficult to compare financial information from different studies, as each reference may vary in the components of transplant included in the financial analysis. Thus, attention should be focused on the percentage reduction in cost or charge associated with outpatient care rather than the exact dollar amounts.

**Shifts in Cost Centers**

Although outpatient BMT care may decrease the overall cost of transplantation, certain departments, such as the pharmacy department, may experience a shift in cost centers rather than an overall reduction in cost. For example, the pharmacy at the University of Nebraska experienced approximately a 20% reduction in BMT-associated pharmacy costs over a 2-year period; however, the inpatient pharmacy noted a 60% reduction, while the outpatient pharmacy noted a 100% increase in BMT-associated pharmacy costs.[34] This shift was due primarily to the implementation of an early transfer from the inpatient to outpatient approach. Similarly, Rizzo et al reported that the reduction in inpatient facility charges in patients receiving care in their comprehensive outpatient BMT program ($67,000 reduction per patient) was largely offset by an increase in outpatient facility charges ($54,000 increase per patient).[16] Even though hospital and overall charges appear to be reduced in an outpatient program, cost-shifting must be acknowledged and addressed when establishing an outpatient BMT program. In the traditional inpatient BMT model, the cost of hospitalization represents the highest percentage of allocated resources. In a financial analysis of resource allocation in our outpatient transplant program, we found that the cost of outpatient staff, injectables, and operating overhead represent most of the direct and indirect costs per patient (Figure 3).[53] Such shifts in cost centers and distribution of resources must be considered for program development and budgeting strategies during the implementation of an outpatient BMT program.

**Cost-Shifting to Patient and/or Caregivers**
Another concern regarding the pharmacoeconomic impact of outpatient BMT care is the potential for cost-shifting to the patient and/or caregivers. Rizzo et al addressed this concern by surveying patients who survived for 1 year after either inpatient or outpatient BMT.[16] Among patients who responded to the survey, no significant difference was noted between those undergoing traditional inpatient or comprehensive outpatient care in terms of out-of-pocket expenses for transportation, lodging, meals, household assistance, child care, or medical expenses. The groups were also similar with respect to reported income lost, involuntary retirement or unemployment, or months of disability. This report suggests that although costs may be shifted to the outpatient facility, there does not appear to be any substantial cost-shifting to or financial burden on the patient.

**Quality-of-Life Data**

Several prospective and retrospective studies have evaluated the quality of life of patients following BMT.[54-57] Most studies have focused on quality of life within the first year following transplantation, and have noted increases in global quality of life by 1 year post-transplantation for the majority of patients. Although many programs suggest that quality of life during the early post-transplant period is better in patients undergoing outpatient care than in those managed in the traditional inpatient model, comparative data documenting such an improvement in quality of life are lacking.

Lawrence et al evaluated symptom distress in BMT patients in the outpatient environment.[58] In this prospective study, patients were asked to give their perception of 12 symptoms at four time points during BMT, including the day of discharge from the hospital following inpatient administration of high-dose chemotherapy and several days after discharge to the outpatient setting. Patient satisfaction and compliance were also assessed prior to final discharge from the BMT program. Fatigue, nausea, insomnia, anorexia, and bowel problems caused the most distress on the first and ninth days of care in the outpatient setting. However, the severity of distress caused by these symptoms was comparable or less than that reported on the day of hospital discharge. The majority of patients had favorable reactions to their outpatient experience and preferred the outpatient environment to the inpatient setting.

Other ongoing quality-of-life studies are evaluating the outpatient environment using validated quality-of-life assessment tools, such as the Functional Assessment of Cancer Therapy–BMT (FACT-BMT) or the City of Hope Quality of Life–BMT (QOL-BMT) questionnaires. These multidimensional assessment tools include evaluations of physical, social, psychological, and spiritual well-being. In future quality-of-life studies, it will be essential to address other aspects affecting quality of life, such as financial burdens imposed on the patient and caregiver. Such data are needed to comprehensively evaluate the benefits of outpatient care during BMT and facilitate an understanding of the risks vs benefits of such care.

**Conclusions**

With the appropriate resources and specifically trained medical and nursing staff, selected patients can now undergo high-dose chemotherapy and autologous PBSC transplantation in an outpatient setting. However, in order to perform these procedures safely, a multidisciplinary team is required to facilitate care and provide services traditionally available only on the BMT inpatient unit. Multiple care environments, including specially designed outpatient clinics and inpatient transplant units, are also essential, as are adequate home health services and reliable, nearby housing. Several models of outpatient BMT care exist; each of these adapts and extends the concept of outpatient care to the local center and environment.

As our experience with outpatient BMT grows and supportive care strategies evolve further, more patients will become candidates for outpatient care. Initially, these procedures were restricted to selected patients with breast cancer undergoing high-dose chemotherapy and autologous transplantation. Currently, in many outpatient programs, selected patients with lymphoma, multiple myeloma, breast and ovarian cancers, and acute leukemias undergoing autologous transplantation are also being successfully treated in an outpatient setting. In addition, allogeneic transplantation is now being performed in younger patients as an outpatient procedure at selected centers. This approach may expand further with the use of nonmyeloblative preparative regimens and donor leukocyte infusions, which result in shorter periods of neutropenia and thrombocytopenia than do conventional allogeneic grafts.
The primary goal of performing BMT procedures in the outpatient setting today and in the future is to adapt our technology and expertise to a clinical setting that ultimately improves patient outcomes and quality of life and uses medical resources in an optimal manner.

References:


16. Rizzo DJ, Vogelsang GB, Krumm S, et al: Outpatient BMT for hematologic malignancies:


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