

ORIGINAL ARTICLE

Autologous hematopoietic stem cell transplants that utilize total body irradiation can safely be carried out entirely on an outpatient basis

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Outpatient hematopoietic stem cell transplants (HSCT) are usually performed in patients receiving minimally mucotoxic preparative regimens; total body irradiation (TBI)-based regimens typically are excluded. To improve resource utilization and patient satisfaction, we developed a totally outpatient HSCT program for TBI regimens and compared outcomes for our first 100 such transplants to 32 performed as in-patients during the same interval, for caregiver or financial reasons. Symptoms were managed predominately with oral agents; pain management consisted of transdermal fentanyl and oral morphine solution. Except for more unmarried in-patients, the two groups were matched. Time to engraftment, severity of mucositis and transplant duration were identical for the two groups. Twenty-seven of the outpatients were admitted (median-6 days), primarily for progressing infection. Thus 92% of all transplant days were outpatient. There were no septic episodes or hospital admissions for pain management. There were no deaths to day 30 in either group and 100-day survival was identical. There was a mean cost savings of \$16000 per outpatient transplant and outpatient patient/caregiver quality of life was similar to that reported for in-patients. Patients undergoing severely mucotoxic regimens can be safely transplanted in an outpatient setting with a significant cost saving, with no increase in morbidity or mortality.

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Introduction

Over the past 15 years there has been a gradual shift in the care of patients undergoing hematopoietic stem cell

transplantation (HSCT) from the in-patient to outpatient setting. With the development of less mucotoxic preparative regimens, approximately 10 years ago several groups began to explore the feasibility of performing HSCT at least partially on an outpatient basis.^{1–8} The initial strategy was to administer the preparative regimen in the outpatient setting with subsequent admission for follow-up care for patients diagnosed with breast cancer. More recently, select patients diagnosed with lymphoma and multiple myeloma have been successfully autotransplanted completely in the outpatient setting, utilizing non-total body irradiation (TBI)-based regimens. The same is true in very select instances for patients undergoing allogeneic transplants.^{2–8}

This shift of care has also occurred owing to improvements in supportive care, as well as cost and quality of life (QOL) issues. The main drivers of this change were the use of peripheral blood rather than bone marrow stem cells, and improvements in supportive care (i.e., antibiotic algorithms, antiemetic regimens and transfusion protocols).¹ It has also been documented that outpatient transplants are associated with a decrease in medical costs,^{1,2,8} and QOL for the patient and caregiver is higher when transplants are conducted on an outpatient basis.^{1,3,9}

Although outpatient autologous transplants have become more common, they are typically limited to patients receiving chemotherapy only preparative regimens that are minimally mucotoxic, based on the impression that patients receiving mucotoxic regimens like TBI would not be able to take oral medications, would have a higher complication rate than in-patients or have inadequate pain control when away from the center each evening. To improve patient satisfaction and resource utilization, in 1997 our center developed a comprehensive care protocol for our outpatient transplant center that included performing all autotransplants when feasible in a totally outpatient setting. This included patients receiving TBI who are the subject of this retrospective analysis. The goal of this analysis was to determine the clinical outcome for this patient group as well as their and their caregiver(s) QOL, and to evaluate any cost saving that might be realized. To do this, we compared 100 such patients to all of those who received TBI-based preparative regimens on an in-patient basis during the same period of time.

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Patients and materials

Selection of patients

One hundred consecutive patients, who underwent an autologous HSCT utilizing a TBI-based preparative regimen at our institution from October 1997 to August 2001, are the subjects of this analysis. Included cancer diagnoses were: non-Hodgkin's lymphoma, Hodgkin's disease, myeloma, acute lymphoblastic leukemia, acute myeloid leukemia (AML), chronic lymphocytic leukemia and chronic myelogenous leukemia (CML). During this period, an additional 32 patients underwent an in-patient HSCT using TBI conditioning. Transplants were conducted on an in-patient basis rather than an outpatient basis if patients chose to do so in the hospital (12), had no caregiver to attend to their health care needs when away from the center (four) or because of financial and/or insurance restrictions (16). To be eligible for outpatient care, patients had to be less than 71 years of age, have an ejection fraction >0.45 obtained by radionuclide scan, had either or both a FEV1 or DLCO >60% of predicted, a measured or estimated creatinine clearance >60 ml/min, and a bilirubin <2.0 mg%. All patients were enrolled on Loyola University Medical Center Institutional Review Board (IRB) autologous stem cell therapy clinical trials that were not specific to location of transplant and signed consent forms for this treatment. Permission was granted by IRB to conduct this retrospective analysis.

Unit care protocol

The patients were cared for in a specifically designed outpatient transplant unit that occupies a portion of the ground floor of the Cancer Center building, and is physically separated from both the in-patient transplant unit and the outpatient chemotherapy area. The unit is a 12-bed facility, with in room electronic vital sign monitoring capability connected to a central nursing station that provides care up to 12 h/day (0700 to 1900), year round, and is specifically designed for patients undergoing bone marrow/stem cell transplants. The unit is in a building that is equipped with an on site lab, radiology suite and chemotherapy pharmacy. Patients stayed in the unit each day only as long as necessary to provide nursing/physician assessment, routine lab tests, transfusions, daily antibiotics and radiographs. This program was designed as a nursing care unit with primary care provided by unit nurses and transplant nurse practitioners with physician oversight. However each patient in both the in-patient and outpatient settings were seen and evaluated by an attending physician at least once daily who for outpatients directly evaluated the progress of the patient that day and approved the nightly discharge after discussion with the nursing team. Any medical care issues during the hours off the unit were made by the attending physician.

The unit was designed to treat patients from the start to completion of transplant with total management of nearly all transplant complications including benign arrhythmias, fever with neutropenia, anemia and thrombocytopenia requiring transfusion support, systemic fungal infections requiring intravenous therapy, pain owing to severe

Table 1 Indications for in-patient hospitalization for outpatient transplant patients

1. Sepsis requiring pressors
2. Temp > 39° in neutropenic patient with active infection
3. Pain uncontrolled with oral morphine and transdermal fentanyl
4. Unable to ambulate without assistance
5. Caregiver illness or fatigue
6. Active GI bleeding: bloody emesis or melanotic stool
7. Mental status changes of confusion or disorientation
8. Oxygen saturation <90% associated with tachypnea
9. Any new pulmonary infiltrate with fever
10. Any acute ECG changes
11. Uncontrolled emesis or diarrhea > 1.5 l in any 8 h interval
12. Progressive hepatic (bilirubin >4.0 mg/dl) or renal (creatinine clearance <50 ml/min) dysfunction

Abbreviations: ECG = electrocardiography; GI = gastrointestinal.

mucositis and non-life threatening infections. Patients are admitted to the in-patient unit only for care that would typically be provided in an ICU (Table 1), for example, active gastrointestinal (GI) bleeding, O₂ saturation less than 90% owing to a progressing pneumonia, hypotension with or without cardiac arrhythmia, uncontrolled diarrhea > 1.5 l/8 h interval or progressive hepatic (Bili >4.0 mg/dl) or renal dysfunction (creatinine clearance <50 ml/min). However, admissions are also permitted for non-compliance or the loss of caregiver support.

All housing was off-site. Outpatients were required to reside within 45 min of the center and to be with a caregiver at all times when not in the unit, to assist with care and to ascertain the need for prompt medical attention. Patients whose primary residences were more than 45 min away obtained substitute, local housing arrangements. Before daily discharge, nursing staff assessed patients to determine discharge status based on the above criteria. Lay caregivers (i.e., family member or friend) provided nightly care which consisted of administering any intravenous antibiotics and assisting the patient administering oral medications and monitoring blood pressure, temperature, pulse, and intake and output readings whilst away from the unit. They underwent training and were expected to monitor infusion pumps at night if in needed. Homecare nursing staff was on call each evening, available to care for patients at home when needed. They received nightly reports by the outpatient unit nursing staff, at the end of each day. Unit nurses reviewed the vital sign parameters to follow at night with the patient's caregiver, including readings that should generate a call to the home nursing shift on call. The physician on call and his phone number was identified each night for the patient.

The program was set up to be as patient and caregiver friendly as possible. All meals if desired were provided to the patient and caregiver on site each day, without additional cost and any oral or intravenous medications that were required overnight were provided without additional cost. Written instructions for the administration of all medications and for collecting vital signs were provided each night. In addition, out of pocket costs were minimized for these patients. In addition to meals and medications any home care visits were covered as part of our contracted transplant reimbursement from the payers.

For patients who lived less than a 45 min drive from the hospital, there were no additional direct patient costs if they chose to have an outpatient transplant. For those who lived more than 45 min from the center, housing was required and not provided, although financial assistance was available based on need that covered up to 25 days of housing. The major indirect cost for outpatient transplant patients was for assistance provided by caregivers. No funds were paid to support this activity.

Preparative regimen administration

All patients received 12Gy of TBI in eight fractions over 4 days from days -8 to -5 with either etoposide (60 mg/kg; day -4) and cyclophosphamide (100 mg/kg; day -2) in combination or on days -6 to -3 with melphalan (140 mg/m²; day -2). Patients received TBI twice daily, separated by a minimum of 5 h and were premedicated with oral lorazepam (1 mg) and oral ondansetron (8 mg). Patients' hemoglobin levels were kept >10 g/dl during the TBI period. On the day of high dose cyclophosphamide administration, patients underwent continuous bladder irrigation for 12 h at a rate of 500 ml/h during and 4 h after the cyclophosphamide and then at 250 ml/h until completion. In addition they received IV fluids after the 12-h period through a portable infusion pump with MESNA at a dose of 1.6 times the cyclophosphamide dose at 200 ml/h over a 14-h period.

Peripheral blood stem cells were cryopreserved and reinfused as reported previously,¹⁰ without the administration of premedications, a minimum of 36 h after the completion of the preparative regimen. No more than three stem cell units were administered per day.

Supportive care protocol

All nutrition was orally administered for both outpatients and in-patients undergoing autologous HSCT, with high calorie liquid supplementation provided for periods of mucositis and nausea. For mild to moderate pain, patients receive 1–2 propoxyphene 65 mg capsules orally every 4–6 h. Patients with moderate to severe pain were treated with transdermal fentanyl (25 mcg/h with appropriate dose escalation) every 3 days with concentrated oral morphine sulfate solution (10–20 mg) administered every 2 h as needed.

The antiemetic regimen consisted of oral ondansetron and dexamethasone during the preparative regimen and lorazepam or prochlorperazine as needed after it was completed. Oral antimicrobial prophylaxis consisted of fluconazole (200 mg b.i.d.), norfloxacin (200 g b.i.d. and initiated at preparative regimen onset), acyclovir (400 g b.i.d.) and trimethoprim/sulfamethoxazole (one double-strength tablet twice a day, on Saturday and Sunday). Ambulatory pumps provided hydration and electrolyte replacement nightly (maximum volume provided was 3 l/14–16 h in a single bag) during and 2 days after high dose cyclophosphamide and beginning on the first day of neutropenia (neutrophil count <500/ μ l) and continuing throughout the neutropenic period. All transfusions were administered whilst patients were in the unit. Patients unable to swallow tablets owing to their mucositis had their

oral meds changed to suspension and if necessary received them intravenously during the day by bolus and if needed at night mixed into their home IV fluids. Prophylactic pooled, irradiated platelet transfusions were administered during the day for counts <20 000/ μ l, and red cells were transfused for a hemoglobin <8 g/dl.

Imipenem/cilastatin 500 mg was administered to neutropenic febrile patients ($\geq 38.5^{\circ}\text{C}$) every 8 h after appropriate cultures were taken. In the absence of hypotension, no patient was admitted for febrile neutropenia, even if it occurred at night or during a period of severe mucositis. For patients with true penicillin allergies (anaphylaxis or angioedema), tobramycin 5 mg/kg qd was administered in combination with vancomycin 1 g every 12 h. Tobramycin/vancomycin levels were obtained around the third dose to identify whether or not the doses were therapeutic. All patients had a 'first dose' of antibiotics available on site at home at the completion of the preparative regimen. Those who developed their first neutropenic fever after leaving the unit for the day were not admitted but were managed on site at their place of residence. If vital signs were stable at the onset of the fever, the home nurse on call was dispatched, drew cultures and initiated the first dose of antibiotics on site (within 45 min of first fever). Over the next 60 min frequent vital signs were obtained and if the patient continued to remain stable, they were permitted to stay at their residence. A chest X-ray was then obtained in the morning to complete the testing. The caregiver administered subsequent nightly doses of antibiotics. For persistent fevers >39°C augmented gram-negative coverage was added and if persistently febrile for >5 days, amphotericin-B at 0.5–1.0 mg/kg was initiated during the day whereas in the unit after an initial test dose.

Patients were discharged to the clinic when they were afebrile, when their absolute neutrophil count $\geq 500/\mu\text{l}$, when their fluid intake was >1.5 l/day, and when their oral calories were $\geq 1500/\text{day}$.

In-patient comparison group

During the interval of this analysis, all potentially eligible patients for an outpatient autologous transplant utilizing TBI who underwent their transplant on an in-patient basis owing to caregiver or financial issues served as a comparison group. They underwent the same preparative regimens, and supportive care protocols as outlined above. Comparisons of demographics, outcome, complications and QOL were performed.

Assessment of QOL

Patients and their caregiver completed measures that assessed QOL, patient satisfaction with care and caregiver burden. All measures used in the study have established adequate validity and reliability and have been used with oncology patients, including HSCT, in the past. QOL and adaptation of the patient and his/her caregiver were measured with the Psychosocial Adjustment to Illness Scale – Self Report (PAIS-SR). The PAIS-SR is a 46-item questionnaire designed to assess QOL and psychosocial adaptation to a current medical illness and its after effects.¹¹ The PAIS-SR has versions for both the patient

and caregiver and seven domains of functioning are measured; health care orientation, vocational, domestic and social environment, sexual and family relationships and psychological distress. Items are rated on a four-point scale; higher ratings indicate poorer QOL and adaptation. Patients (only) completed the Family Adaptation, Partnership, Growth, Affection and Resolve (APGAR) Scale. This scale is a brief five-item tool to measure the patient's level of satisfaction on help received from his/her caregiver, discussion of problems, acceptance of activities and lifestyle, expression of emotions and time spent together.¹² Scores for the Family APGAR Scale range from 0 to 10 and higher scores indicate greater satisfaction. Caregivers (only) completed the Caregiver Impact Scale. This scale measures the caregiver's report of objective burden (e.g., the effect of caregiving on his/her daily life, personal time, finances) and subjective burden (e.g., attitudes and emotions about caregiver role) associated with providing care to the patient. Items are rated on a five-point scale and higher scores indicate greater perceived burden.¹³ The Caregiver Impact Scale is also known as the Measurement of Burden Scale, we renamed the scale for this study in order to reduce possible negative connotations associated with the concept of 'burden'.

Statistical analyses

The in-patient and outpatient groups were analyzed for demographic factor differences as well as complications post transplant. All comparisons were carried out using the χ^2 test. Survival analyses were carried out using the method of Kaplan and Meier. To examine changes over time for QOL and psychosocial parameters, one-way repeated measures analysis of variance were used.

Results

Clinical outcomes

During the period of analysis 100 consecutive patients underwent an outpatient autologous HSCT using TBI-based preparative regimens, starting with the first patient transplanted with TBI in the unit. There were 32 in-patient transplants that utilized TBI performed during this interval for caregiver issues (lack of or unwilling) in 16 or financial (unable to provide for housing needed during the period of confinement) or insurance issues in 16. In particular nine Medicaid recipients were required to be transplanted in the hospital under the State of Illinois transplant program during the period of the study.

Patients in the two groups were matched for: median age, percentage of PR1/CR1, sensitive relapse, refractory disease, type of disease, number of prior regimens, performance status, pretreatment albumin, median CD34+ cells/kg and median days from diagnosis to transplant (Table 2). In addition, there were no differences in the two groups based on the Hematopoietic Cell Transplantation-specific Comorbidity Index¹⁴ (Table 2). The median Southwest Oncology Group (SWOG) performance status was 1 in each of the two groups. The only significant difference between the two groups was that there were a significantly higher number of single patients (56% vs 17%) transplanted in the hospital ($P < 0.001$).

The transplants were performed safely in either setting. There were no treatment-related deaths in the first 30 days after transplant in either group. Although severe (World Health Organization (WHO) grade III/IV) mucositis was seen in all patients, none were admitted to the hospital for pain control, or for initial evaluation of febrile neutropenia. Of the 100 outpatients, 72 remained completely outpatient,

Table 2 Characteristics of patients undergoing outpatient vs in-patient transplants

Clinical characteristics	Outpatient (N = 100)	In-patient (N = 32)	P-value
Median age	50	47	NS
Single	17%	56%	0.05
Male	49%	63%	NS
CR1/PR1	24%	26%	NS
Sensitive relapse	59%	56%	NS
Refractory disease	14%	15%	NS
<i>Diagnosis</i>			
Non-Hodgkin's	74	27	NS
Hodgkin's	12	4	
Myeloma	4	0	
Other (AML, ALL, CML, CLL)	10	1	
Median # of prior regimens	2	2	NS
Pretreatment albumin (g/dl)	3.8	3.7	NS
Median CD34+ cells/kg transplant dose	3.8×10^6	3.9×10^6	NS
Median days from diagnosis to transplant	701	643	NS
<i>Comorbidity Index Scores¹⁴</i>			
0	51%	46%	NS
1	12%	24%	
2	12%	6%	
3	10%	12%	
4 or higher	3%	3%	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CR = complete remission; PR = partial remission; NS = nonsignificant.

with 28 admitted for progressive infection during neutropenia (11), caregiver issues (six), GI bleeding during thrombocytopenia (four), cardiac arrhythmias (two) and severe diarrhea with dehydration, seizure, allergic drug reaction, weather and a fall at home (1 each). There were no admissions directly from home with the exception of the patient who slipped and fell on his steps coming to the center in the morning. This patient was diverted to the emergency room (ER) and was admitted directly from there. Febrile neutropenia with these regimens was universal; approximately 1/3 of all febrile neutropenia occurred in the evening hours. All patients received their first dose of antibiotic within 60 min of the first call and in no cases were patients admitted as no hypotensive episodes were observed, similar to those who developed their fever in the outpatient unit. The median length of in-patient hospitalization was 6 days, with 13 (46%) admitted for 4 days or less, 10 between 5 and 10 days and six for more than 10 days. The admission rate during the first 2 years was 37%; however, this dropped to 17%, for the last 2 years of the analysis. Overall only 168 of a potential 2100 days (8.0%) were spent in the in-patient unit for those undergoing an outpatient transplant.

The course of transplantation was similar for patients in the in-patient and outpatient setting (Table 3). The median time to neutrophil and platelet engraftment was the same for the two groups as was the duration of severe mucositis. The number of days of febrile neutropenia was also the same, but there were fewer days of IV antibiotics used in the outpatient setting (10 vs 12 days; $P < 0.001$). Time from initiation to completion of the transplant, defined as engraftment of neutrophils ($> 500/\mu\text{l}$), adequate oral fluid (1.5l/day) and calorie intake (1500 kcal/day) was identical in the two groups (21 days), and the number of platelet and red blood cell transfusions were identical in the two groups.

Survival at 100 days was identical between the two groups (Table 3). However as shown in Figure 1 at a median f/u of 57 months, there were a significantly higher number of patients in the outpatient group alive (65% (95% confidence interval (CI) 58–77) vs 47% (95% CI 27–61); $P < 0.001$). The majority of this difference was due to a higher relapse rate for in-patients (Table 4). To determine if there were any transplant related factors that might account for this difference, the causes of death were determined and are shown in Table 4. As indicated relapse

was the cause of death in 94% of those in the outpatient group and 100% of the in-patient group. The median age for those relapsing in the in-patient group was 49 and in the outpatient group was 48. There were however four patients lost to follow-up in the in-patient group who were later identified as having died via the Social Security database. In contrast none were lost in the outpatient group. In addition, of the 38 relapses in the outpatient group (38%), 13 (34%) underwent an allograft with 5/13 alive and without disease, whereas none of the 19 patients who relapsed after the in-patient procedure were referred for an allograft ($P < 0.01$).

QOL analyses

QOL data are available for 26 patients who received their transplant in the outpatient setting and 32 caregivers of outpatients who completed assessments at all three time points; that is, baseline (i.e., immediately before the start of treatment), the day of transplant and 30 days post transplant. Assessments were obtained from a cohort of in-patients but meaningful interpretation of the data was hampered by small numbers and a lack of statistically significant differences between the two patient groups, therefore only results for outpatients and caregivers are

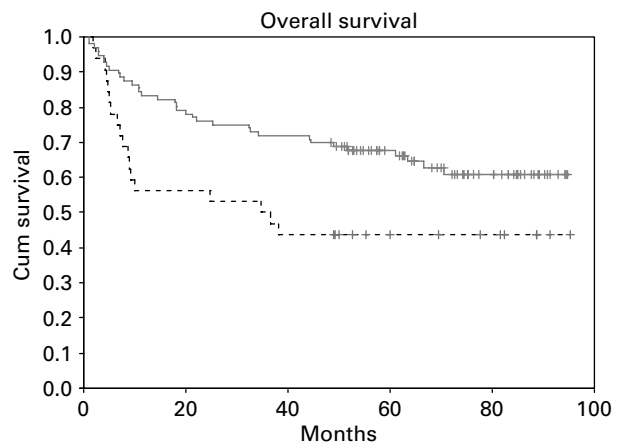


Figure 1 Survival of patients undergoing outpatient vs in-patient autologous HSCT using TBI-based preparative regimens — outpatient; ---- in-patient.

Table 3 Transplant outcomes

Transplant outcomes	Outpatient (N = 100)	In-patient (N = 32)	P-value
Time to ANC $> 500/\mu\text{l}$ (days)	10	11	NS
Time to platelets $> 20\,000/\mu\text{l}$ (days)	12	13	NS
Days of IV antibiotics	10	12	< 0.001
Days of neutropenia (ANC $< 500/\mu\text{l}$)	11	11	NS
Days of WHO Grade III/IV mucositis	4	4	NS
Transplant duration (days)*	21	21	NS
Transplant-related mortality	0%	0%	NS
30-day survival	100%	100%	NS
100-day survival	96%	97%	NS

Abbreviations: ANC = absolute neutrophil count; NS = nonsignificant; WHO = World Health Organization.

*Transplant duration = time from initiation of preparative regimen to discharge.

Table 4 Long-term outcome

	Outpatient (N = 100)	In-patient (N = 32)
Alive, NED (%)	65 (65)	15 (47)
<i>Deaths</i>	35	17
Median age	50	49
Cause of death – relapse	33	17
Cause of death – other	2 (pneumonia, encephalitis)	
Relapses (%)	38 (38)	19 (59)
Allografts after relapse	13	0
Alive, NED post-allograft	5	
Alive with disease	0	2
Lost to follow-up	0	4

Abbreviation: NED = no evidence of disease.

presented. Patients reported significant changes in QOL over time as measured by the PAIS-SR; with a baseline mean score of 35.2 ± 13.6 , worsening of QOL on the day of transplant with a mean score of 41.8 ± 14.7 , and a return to pretreatment level of QOL 30 days post transplant with a mean score of 31.6 ± 14.1 ($P < 0.0001$). A similar pattern of change was noted for caregivers of outpatients that neared but did not reach statistical significance, with QOL returning to pretreatment levels by 30 days post transplant (baseline 34.3 ± 13.7 ; day of transplant 38.9 ± 16.5 ; 30 days post transplant 35.5 ± 17.9 ; $P = 0.057$). Patients' satisfaction with help received from their caregivers was found to be consistently high for all three assessments; with a mean score of 9.3 ± 1.2 at baseline and the day of transplant, and 9.3 ± 1.0 at 30 days post transplant ($n = 26$ outpatients; $P = 0.48$).

Caregiver impact scores indicate there were no significant differences in objective caregiver burden at all three assessments: baseline 32.3 ± 4.6 ($n = 49$), day of transplant 33.4 ± 5.6 ($n = 47$), and 30 days after transplant 32.4 ± 5.1 ($n = 30$; $P = 0.30$). Likewise, there were no significant differences for subjective caregiver burden at all three assessments: baseline 21.9 ± 5.2 ; day of transplant 21.8 ± 5.4 and 30 days post transplant 22.8 ± 7.0 ($P = 0.12$).

Cost analysis

A cost analysis was performed to determine if there were any direct cost savings for the outpatient group. Patient charges were collected for both cohorts of patients from admission to discharge from either the in-patient or outpatient unit. Using our institution's Medicare cost to charge ratio, there was a mean saving of \$16 000 per transplant performed on an outpatient basis. However, these savings were largely attributed to the 72% who completed the transplant entirely on an outpatient basis, with no cost difference for those who started outpatient and required admission as compared to those totally performed in-patient. The cost savings with no increase in life-threatening complications has led the State of Illinois to now permit Medicaid patients to be transplanted in the outpatient setting. This analysis did not include indirect costs borne by the patient and/or family for lodging, transportation or any caregiver costs.

Discussion

Outpatient HSCT has been performed in three ways: an early discharge model, that is, after the preparative regimen is completed, a delayed admission model, that is, after the preparative regimen is completed, and a totally outpatient model.¹ As the third model optimizes bed utilization for inpatient units, it was chosen for our program. Our goal was to eliminate all contraindications to outpatient transplantation but we found, as have others, that financial and/or insurance restrictions, lack of a qualified caregiver, patient/family refusal/lack of comfort with outpatient care and psychological factors limit the use of outpatient HSCT to 70% of eligible patients.^{1–3}

We now show that even for the most mucotoxic regimens, control of symptoms related to the preparative regimen and life-threatening complications is as good in the outpatient setting, and that despite febrile neutropenia in all patients, they can be safely treated and monitored at home at night under the cover of intravenous antibiotics and fluids. Our comparison demonstrates that based on identical engraftment rates, a 0% mortality rate, timely completion of the transplant procedure and identical 30 and 100 day survival that TBI-based autologous HSCT can be safely carried out completely on an outpatient basis. Required hospital stays for complications are short, with most patients requesting early discharge frequently before the problem which led to their admission was resolved.

TBI-based preparative regimens have been administered in the outpatient setting previously, with Bredeson *et al.* reporting the largest series.^{15–16} They showed that the administration of outpatient TBI was safe in 142 patients; however, approximately 50% of the total days of transplant were provided in the in-patient unit (vs 8% here) and in his study 56% received less than 12 Gy of TBI. The percentage of those who received 12 Gy who were able to continue their transplant on an outpatient basis was not provided.

Other reports document the safety of managing HSCT complications in the outpatient setting, including febrile neutropenia after high-dose chemotherapy alone regimens.^{4,8,17} Although 70% of our patients vs 36% of Jagannath *et al.*'s⁸ patients underwent an outpatient transplant for those that did the admission rate and number of in-patient days was similar in the two studies although none of our patients were admitted for febrile neutropenia in the absence of progressive infection. This favorable outcome is similar to a matched pair analysis of 51 autografts who received high-dose chemotherapy alone and HSCT by Hermann *et al.*,¹⁷ and another small series of 13 patients who received essentially all care at home after stem cell re-infusion.¹⁸ The combined results indicate that febrile neutropenia, and uncontrolled infection are not increased in patients transplanted in the outpatient/home setting and thus episodes of septic shock would be expected to occur only rarely. Our data confirm the safety of the home care of HSCT patients to those receiving to severely mucotoxic regimens.

QOL and psychosocial data from this sample suggest that decrements in QOL were mild and transient. Interestingly, the patterns of adjustment and QOL were very

similar for patients and caregivers, with the time of greatest difficulty occurring around the day of transplant and thereafter improving. Overall, patients were highly satisfied with the care they received from their caregivers, and caregivers' experience of burden was unchanged over the immediate course of HSCT (i.e., pretransplant through day 30 post transplant), despite the severe mucositis that all patients experienced. Our patients and their caregivers' QOL scores were comparable to scores reported for in-patient samples.^{19,20} In addition our outpatient caregivers did not perceive their burden to be any greater than caregivers of in-patients. However, these results are preliminary and therefore interpretations should be made cautiously.

The cost saving from outpatient transplantation has been previously documented for minimally mucotoxic regimens.^{2,5,8,21} Meisenberg *et al.*⁵ conducted a financial analysis comprising 94 patients receiving a HSCT in the traditional in-patient, partial outpatient or total outpatient setting. There were no differences between the groups in age, diagnosis, or performance status before high-dose chemotherapy, or the rate of fever, days on antibiotics, number of transfusions, length of neutropenia or toxicity. Similar to our findings the cost saving was significant only for those performed totally on an outpatient basis with the median costs per patient being \$37 900, \$36 200 and \$29 400 for the in-patient, and partially and totally outpatient groups, respectively. Our savings appeared higher, which could be due to a variety of factors including local costs, the dates of the analysis and perhaps due to the intensity of the preparative regimen used.

Cost shifting to families and caregivers does occur for outpatient transplants and may be a concern to the patients and their families. We did not collect this data or costs of educating caregivers in patient management issues at night. However this training was performed using existing staff on a daily basis. In their report, Jagannath *et al.*⁸ did consider such costs in their analysis and estimated that costs for medications, housing, meals and lost wages for the caregiver needed for outpatient transplants to be approximately \$4000 per transplant. Our indirect costs should have been lower however as we included without additional costs to the patient or caregiver all intravenous and oral medications not administered in our outpatient unit, as well as all meals for both the patient and caregiver(s), and any homecare visits during the transplant period. In addition, we did not require patients to live in university managed housing if they lived in the Chicago area. Thus out of pocket housing costs for both local as well as distant transplants should be low for both groups as housing is still needed for caregivers of in-patients traveling from a distance to reside in during transplant. It is important to note that Rizzo *et al.*²¹ also evaluated all costs for the first 70 days for a mixture of both allogeneic and autologous transplants performed on an outpatient basis, and found no difference in out-of-pocket expenses for such items as expenses owing to employment changes, transportation and lodging, as well as the costs we covered including medications, meals and any required home care visits during the transplant period in the outpatient transplant group. Nevertheless the loss of income that may result from

a caregiver's having to take a leave of absence from work may be significant in individual cases, and was a factor in 16 of out patients eligible for outpatient HSCT.

Although survival at 100 days was identical in the two groups, we found a higher long-term survival for those having an outpatient transplant. The groups were matched by disease status, comorbidity index and chemosensitivity pretransplant, and the median age of those who died was identical in the two groups. There was however a lower relapse rate for those transplanted on an outpatient basis and five of these appear to be long-term survivors after an allograft as compared to none in the in-patient group which likely explains the difference in survival. None of the in-patients who relapsed underwent an allograft vs 34% of the outpatient group, and interestingly, many of these patients did not continue close follow-ups at the transplant center, suggesting there may have been subtle qualitative medical, psychosocial and/or financial differences in those undergoing in-patient transplants. Long-term survival differences have been noted previously for allogeneic HSCT patients based on financial well being. Although there were no differences for 14 underinsured-poor patients to 100 days, Selby *et al.*²² did find an increase in mortality of 50 % vs 15% ($P=0.027$) from 100 days to 6 years, despite no differences in the other prognostic factors between this group and the insured, 'non-poor' group who underwent allografts for AML and CML. We are attempting to quantitate and rectify this difference in ongoing patients.

Our successful outpatient HSCT program was made possible by a close working relationship between the patient, caregiver, nursing staff in the unit and at home, and the physician and the development of comprehensive protocols for infections, hydration, nausea, pain and complication management. In doing so, we are able to provide cost-effective transplants with no increased risk of life-threatening complications. The program grew during the period of the study, permitting us to perform additional allografts in the in-patient unit. With the verification that outpatient transplants are safe, more payers should participate in this type of program and consider supporting the uncovered costs for patients and families. In fact the State of Illinois now permits Medicaid patients to be transplanted on an outpatient basis.

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