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ORIGINAL ARTICLE

Outpatient myeloablative allo-SCT: a comprehensive approach yields decreased hospital utilization and low TRM

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Historically, myeloablative allogeneic hematopoietic SCT (HSCT) has required prolonged in-patient hospitalization due to the effects of mucosal toxicity and prolonged cytopenias. We explored the safety and feasibility of outpatient management of these patients. A total of 100 consecutive patients underwent a matched-related donor myeloablative allogeneic HSCT for a hematologic malignancy at a single institution. Patients were hospitalized briefly for stem-cell infusion and thereafter only for complications more safely managed in the in-patient setting. The median hospital length of stay from the start of the preparative regimen to day +30 and day +100 post-transplant was 12 and 15 days, respectively. Planned hospital discharge occurred in 79 patients after stem cell infusion. Patients were readmitted to hospital at median of day +7 post transplant, with neutropenic fever being the primary cause for readmission. In total, 18 patients required no in-patient care in the first 100 days. Non-relapse mortality at day 100 and 6 months was 10 and 15%, respectively, for all patients, and 0 and 5%, respectively, for standard risk patients. In summary, outpatient myeloablative allogeneic HSCT with expectant in-patient management can be accomplished safely with low treatment-related morbidity and mortality. Clinical outcomes seem comparable to those reported for traditional in-patient management.
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Introduction

Myeloablative allogeneic hematopoietic SCT (HSCT) provides potentially curative therapy to patients with life-threatening hematological malignancies. Its efficacy depends both on the ability to deliver intensive chemotherapy and/or radiation, as well as the immunotherapeutic effect of donor immune cells (graft vs malignancy effect). Although studies consistently show lower recurrence rates compared with autologous HSCT or conventional chemotherapy approaches,[1–3] potential benefits are often negated by the accompanying high incidence of transplant-related morbidity and mortality.

After myeloablative chemoradiotherapy, mucosal toxicity and prolonged cytopenias lead to a significant risk of infectious complications, including bacterial, invasive fungal and viral infections. The severity of these complications has historically mandated in-patient delivery of care, and patients are traditionally hospitalized during the high-dose preparative regimen until hematopoietic recovery and resolution of mucosal toxicity, with median length of initial hospitalization ranging from 25 to 30 days.[4–6] During the pancytopenic phase, patients are typically kept in a protective low-pathogen environment with the use of HEPA (high-efficiency particulate air) filtration systems.

With advancements in supportive care, transplant programs are beginning to explore strategies to reduce hospital length of stay by moving all or part of transplant management to the outpatient setting. It is hoped that efforts to decrease hospital utilization may translate into improved patient satisfaction and quality-of-life, reduced exposure to nosocomial pathogens, lower costs and reduced pressure on available beds. Several groups have shown that autologous HSCT can be safely delivered in the outpatient setting with good outcomes and diminished cost.[7–15] In addition, allogeneic transplantation after nonmyeloablative conditioning also seems feasible in the ambulatory care setting,[16–18] given its significantly reduced regimen-related toxicities compared with standard allogeneic HSCT. A few pilot studies have explored the safety of outpatient myeloablative allogeneic HSCT[4,19] in small numbers of selected patients, but none have documented whether this approach is generalizable to the majority of patients requiring such therapy.

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We have developed a comprehensive outpatient management program that is applied to all patients receiving allogeneic HSCT at our center. We report the results of 100 consecutive unselected patients who received a matched-related donor allogeneic HSCT after myeloablative conditioning. We evaluated the impact of outpatient management on safety, hospital utilization and clinical outcomes.

Materials and methods

Patient characteristics

A total of 100 consecutive patients who underwent a myeloablative matched-related donor allogeneic HSCT from January 2000 to February 2006 were included in this analysis. In addition to meeting standard clinical eligibility criteria to undergo transplant, each patient underwent assessment by the clinical team and health psychologist to determine their suitability to initiate transplant care in the outpatient center. Each patient was required to have an approved caregiver(s) available on a 24-h basis from the start of conditioning through day +100 and lodging within a 1 h driving radius of the outpatient clinic during this period. Patients living outside the required distance were required to stay at provided local housing options that included the Winn-Dixie American Cancer Society Hope Lodge, several furnished apartments provided by the program, as well as option to lease extended-stay apartments operated by commercial hotel vendors located within a short distance from the transplant center.

Caregivers were generally relatives or friends, who were required to undergo educational training and subsequently be approved by the transplant team before the patient proceeded forward with the therapy. Their responsibilities included providing updates regarding the patient's compliance to instructions on oral medications, diet and activity, and feedback on symptoms and emotional status. Caregivers were instructed to take the patient's temperature when at home several times daily or when a fever was suspected; and to contact the on-call transplant physician promptly for temperature of 100.5 °F or greater, the development of rigors/chills, recurrent nausea or emesis, the development of significant diarrhea, rash or other significant symptoms. If indicated, the transplant physician would then direct the caregiver to transport the patient so as to admit him or her directly to the in-patient transplant unit. In the unusual situation that the patient is unstable, the patient would be transported by ambulance to the hospital. Similarly, if in the course of evaluation in the outpatient center it is deemed appropriate to admit the patient, they would be admitted directly to the in-patient transplant unit, or to the intensive care unit (ICU) if they were unstable.

For a minimum of 100 days after transplant, the patient was not permitted to drive, to visit indoor public spaces such as shopping malls, restaurants or theaters, and was restricted to a neutropenic diet. The patient and caregiver(s) were instructed in the importance of hand washing and to avoid contact with individuals having viral respiratory or gastrointestinal symptoms. Each patient was expected to stay physically active and to walk up to 1 mile daily or the equivalent exercise activity in both the outpatient and in-patient setting unless unable due to medical condition. Patients were permitted to be outdoors with the use of a traditional surgical mask.

Patients were treated according to a comprehensive outpatient management protocol in which the majority of clinical care, including the administration of high-dose chemotherapy and/or TBI as well as post-transplant supportive care, was planned for delivery in the outpatient setting. Any patient with compliance issues or concerns regarding having appropriate caregiver support, either before proceeding forward with treatment or at any time during the transplant course, was treated according to a more traditional in-patient model of care, with all or a large part of their care delivered in the hospital. These patients are included in this analysis to avoid selection bias. Before transplant, patients received verbal and written education describing the transplant process from the members of our multidisciplinary team including a physician, transplant coordinator, clinical health psychologist and clinical pharmacist. Patient medical care was provided either in the outpatient center or hospital. Home care nursing companies were not used.

Facilities

Outpatient center. The outpatient care facility is dedicated exclusively to the care of HSCT and acute leukemia patients. The facility is located within a 12-story building with enclosed patient parking and direct elevator access to the outpatient transplant patient care suite, and is connected to Northside Hospital by enclosed passageway. The clinic is a 15 000 ft^2 HEPA-air-filtered facility that operates 7 days per week from 0700 to 1700 hours daily. The infusion patient care area has 24 infusion chairs including 7 private isolation rooms, and in addition 4 private negative-pressure isolation rooms. Adjacent area includes three consultation rooms, two large procedure rooms, examination rooms, an on-site pharmacy, clinical hematology–chemistry laboratory, conference room and family–patient lounge area. In total, 4000 ft^2 of the facility is dedicated to the apheresis center, a Food and Drug Administration licensed blood collection facility where PBSCs are also collected. The center includes offices for the transplant physicians and mid-level providers, medical records, pharmacists, administrative support staff and nursing supervisors. An additional 4500 ft^2 of space located in proximity on the same floor of building provides administrative offices for the health psychologist, transplant coordinators, the clinical pharmacists, quality management supervisor, the clinical research, and data support staff team and financial coordinators.

In-patient unit. The BM transplant unit is a HEPA-filtered isolation unit with 17 beds, which includes reverse isolation negative-pressure rooms. The facility includes office space for in-patient nurse practitioners, clinical pharm D staff, nursing supervisor and quality management supervisor. Exercise equipment includes treadmill and stationary bicycle. A caregiver is permitted to stay overnight with the patient with an adjacent pull out bed in every room. A separate ICU facility with HEPA-filtered and reverse isolation negative-pressure rooms are used for

patients who require critical care support including mechanical ventilation.

Transplant support staff and operations

In compliance with Foundation for the Accreditation of Cellular Therapy (FACT) standards, the outpatient and in-patient program are overseen by the program medical director and use the same standard operation procedures for quality management, supportive care, treatment protocols and continuing education where applicable. Both the facilities have dedicated nursing, mid-level and ancillary staff team who are required to participate throughout the year in programmatic training and education. All nurses must complete comprehensive training in the care of transplant patients, and in general are OCN certified. The nursing ratio for the in-patient unit is 1:3 and the in-patient mid-level to patient ratio average is approximately 1:12. Owing to potential fluctuations in in-patient census, the in-patient transplant nurse staffing is maintained in a surplus status to accommodate high census overflow. During times of a lower census, the excess nurse(s) are rotated on the adjacent medical oncology unit and medical ICU.

The outpatient nurse-to-patient ratio is 1:5 and the mid-level-to-patient ratio average is 1:10, in addition to scheduled procedures and patient consults. The outpatient mid-level performs a comprehensive assessment and examination of the patients on each visit including a psychosocial assessment, as well as verifying compliance to both oral medications and patient care guidelines including diet, activity, reporting of symptoms and temperature monitoring. A total of five clinical Pharm D staff is assigned to the transplant and leukemia combined program. One Pharm D is assigned to the allogeneic outpatient transplant program, and along with the clinical team verifies with the patient and caregiver on each visit that the patient is taking their medications correctly, monitors medication drug levels, potential drug interactions, CMV surveillance testing and adverse events. Each week an independent audit is performed by the Clinical Pharm D team to verify that chemotherapy, immunosuppressive and antimicrobial agents have been administered as per institutional guidelines in the allogeneic transplant patients. A dedicated GVHD nurse participates on outpatient rounds to monitor changes in the management and to provide continuity of care between the in-patient and outpatient phases of the patient's care.

The transplant physicians, health psychologist and clinical Pharm D team provide direct clinical care oversight to both the in-patient and outpatient facilities. The transplant physicians are on a rotational 7-day weekly schedule that includes assignment as either the in-patient or outpatient transplant physician who rounds daily on all transplant patients with the assigned mid-levels, clinical Pharm D, health psychologist, nursing staff and ancillary support staff. There is a daily communication between the in-patient and outpatient team regarding admissions and discharges. The in-patient transplant physician is on call 24 h to the transplant unit and is responsible for admissions of outpatients after clinic hours. In the case of an emergency, an in-house rapid response team/physician is available at all times. If a patient is transferred to the ICU, the in-patient transplant physician and team continue to follow-up the patient along with the support by the critical intensive care team. Each week there is a general meeting with nursing representatives from the in-patient and outpatient facilities, physicians, mid-levels, health psychologist and transplant coordinators in which all active transplant patients are discussed. Each patient is assigned a dedicated outpatient mid-level provider who follows up the patient in the clinic until discharge from the program.

The in-patient and outpatient facilities have separate medical charts that are maintained by their respective medical record office. Admission packet and detailed problem list accompanies all admissions to the transplant unit. Similarly, on discharge the outpatient chart is updated in regards to a hospital discharge summary, updated problem list along with the inclusion of hospital laboratory, radiology and pathology data. At the time of hospital discharge, a written medication calendar, discharge instructions and treatment plan is reviewed with the patient and caregiver. Written orders for the outpatient facility are prepared by the Clinical Pharm D, and physician and a treatment plan summary are communicated to the outpatient team. Both facilities have access to the hospital electronic medical record system. A dedicated electronic data system tracks key patient parameters during their treatment course including GVHD management and response, and infectious disease events.

The transplant coordinators participate in organizing the initial referral of patient, pre-transplant phase assessment, discharge planning of the patient back to the referring medical oncologist and long-term follow-up assessments. The staffing ratio is approximately 1 coordinator for every 50 patients referred to the program. The present staffing is at six coordinators.

Conditioning therapy

Patients received a variety of myeloablative preparative regimens containing either full-dose of BU or myeloablative doses of TBI. High-dose chemotherapy was administered i.v. in the outpatient clinic. Mesna was administered in conjunction with high-dose CY and by continuous infusion over 24 h through a CADD (continuous ambulatory drug delivery) device. BU was administered orally at home as previously described,[20] and pharmacokinetic monitoring was performed to target an AUC of 900–1500 μmol/l. Patients were instructed to document all BU administration on a home medication administration record, which was reviewed for completeness by a clinical pharmacist. Verbal and written education regarding chemotherapy and other transplant-related medication was provided by a clinical pharmacist before the initiation of treatment. Standard anti-emetic therapy was provided to the patient. All patients received oral benzodiazepine and prochlorperazine for management of nausea that may occur after being discharged home from the clinic.

Allograft collection and processing

Granulocyte-CSF, 10 mcg/kg s.c. for 5 days, was used as a mobilizing regimen for donor PBSC collection. For each PBSC collection, 15–20 l of blood was processed using the

COBE Spectra. The targeted CD34+ hematopoietic stem cell dose is 5.0×10^6 per kg. A BM harvest was performed in 10 patients. The targeted BM collection dose was 3×10^8 mononuclear cells/kg. Peripheral blood and BM stem cells with minor ABO incompatibilities were plasma depleted and washed using the COBE 2991 cell processor. BM stem cells with major ABO incompatibilities were concentrated and red blood cells were reduced.

GVHD prophylaxis
Tacrolimus 0.03 mg/kg/day or CYA 3 mg/kg/day were administered i.v. by continuous infusion through CADD pump as prophylaxis against GVHD beginning on day −1. MTX 5 mg/m^2 i.v. bolus on day +1, +3, +6 and +11 was also administered in the majority of patients. Immunosuppression therapy, administered i.v. through CADD pump, continued until day +21 in all the patients. Thereafter, patients received the oral equivalent unless they were not able to tolerate oral medication. Tacrolimus and CYA levels were routinely monitored. Tacrolimus doses were adjusted to target a therapeutic level of 10–20 ng/ml and CYA does were adjusted to target levels between 150 and 300 ng/ml. Immunosuppression was tapered beginning day +60 or day +180, based on the patient's estimated risk of relapse.

Post-transplant supportive care
Antimicrobial prophylaxis and CMV monitoring. Beginning the day of transplant, all patients were started on oral prophylactic antimicrobials. An antibacterial, levofloxacin 500 mg/day or gatifloxacin 400 mg/day, was administered and continued until an ANC $\geqslant$0.5 k per μl for 3 days or $\geqslant$1.5 k per μl for 1 day was achieved. For patients with positive HSV serology or history of Varicella Zoster virus reactivation, acyclovir 400 mg twice daily was administered and continued until engraftment. In the setting of earlier Varicella Zoster virus reactivation, acyclovir was continued until immunosuppression was discontinued. Standard antifungal prophylaxis consisted of fluconazole 400 mg daily, which was discontinued at day +75 (day +100 in more recent patients) in the absence of GVHD, neutropenia or corticosteroid use. Patients with earlier history of suspected fungal infections received antifungal prophylaxis with anti-mold coverage such as itraconazole, voriconazole or caspofungin. In the presence of GVHD, antifungal prophylaxis was continued until immunosuppressive therapy was discontinued. Neupogen 5 mcg/kg/day was administered daily beginning day +6 until engraftment. Pneumocystis carinii prophylaxis was initiated day +30 and continued at least 6 months post-transplant and until immunosuppression was discontinued. Quantitative CMV PCR was monitored weekly starting day +14, and preemptive therapy was initiated if viral reactivation was detected using either ganciclovir or foscarnet administered i.v. through a CADD pump in the outpatient setting.

General outpatient monitoring and electrolyte management. Patients were evaluated in the outpatient clinic the morning after being discharged from the hospital and daily thereafter until day +28, unless they required hospitalization. During this time phase in the outpatient clinic, patients generally received 1–21 of normal saline infusion daily along with electrolyte replacement for potassium and magnesium as indicated. A 'dry weight' was established and diuretic therapy was given for significant fluid retention on an as needed basis. For the subsequent 2 months, patients were generally evaluated three to four times weekly. At 100 days post transplant, patients were discharged back home to their referring medical oncologist unless they had adverse events such as active GVHD that required continuation of frequent follow-up in the outpatient center.

Hospital admission and discharge policy
All patients were admitted to the hospital the morning of their graft infusion and monitored for at least 2 h post infusion. Patients were discharged the same day if clinically stable (afebrile, ambulatory and adequate oral intake). Before hospital discharge, instructions about home care were reviewed by the nurse and clinical pharmacist. Patients were again instructed to contact the clinic or the on-call physician for symptoms requiring immediate attention such as fever >100.5 °F, intractable vomiting or profuse diarrhea. A clinical pharmacist provided oral and written education regarding home medications, including a home medicine administration record outlining the medication name, indication, strength and administration directions. At each clinic visit, patients were assessed by a nurse practitioner/physician assistant, pharmacist and physician. Patients were then readmitted directly to the in-patient unit for complications including neutropenic fever, mucositis pain requiring IV medication, reduced oral intake, or uncontrolled nausea or diarrhea. Patients remained in the hospital until complications resolved. It was general practice to keep one to two hospital beds available at all times for expectant admissions.

Definitions and statistical analysis
Disease status was determined to be standard risk (acute leukemia in first CR; CML in first chronic phase; Hodgkin's or non-Hodgkin's lymphoma, CLL or myeloma in first remission, myelodysplastic syndrome or myeloproliferative disease without excess blasts) or high risk (all others) as determined at the time of transplantation. Time to hematologic reconstitution was measured from day 0 to the first of three consecutive measurements of an ANC $\geqslant$500/μl and a plt count $\geqslant$50 000/μl, independent of transfusions.

Overall (OS) and progression-free survivals (PFS) were defined as the time from day of transplant (day 0) to the day of death or disease progression, respectively. OS, PFS, relapse and non-relapse mortality were estimated by the Kaplan–Meier product-limit method.[21] The log-rank test was used to compare differences between patient subgroups. All *P*-values were two-sided, and a *P*-value <0.05 was considered significant.

Results

Patient and transplant characteristics
A total of 100 consecutive patients (median age 44 years (range 21–64 years)) underwent a myeloablative allogeneic

Table 1 Patient, diagnosis and transplant characteristics

% of patients (n = 100)			
Gender		*Diagnosis*	
Male	69	NHL	27
Female	31	AML	25
Age (years)		CML	15
Median (range)	44 (21–64)	ALL	14
Preparative regimen		MM	5
BU/Cy	42	MDS	5
BU/Cy/VP16	34	CLL	3
VP16/TBI	16	HD	2
Cy/TBI	3	MPD	2
Flu/BU	2	PCL	1
Flu/BU/Campath	1	Thal	1
Flu/BU/Melphalan	1	*Disease status*[a]	
BU/Melphalan	1	High risk	60
Stem cell source		Standard risk	40
Peripheral blood	89	*CMV status*	
BM	10	Donor +/recipient +	41
Mixed	1	Donor −/recipient +	36
GVHD prophylaxis		Donor −/recipient −	18
FK-506 + MTX	93	Donor +/recipient −	5
CSA + MTX	3	*Gender mismatch*	
FK-506 alone	4	Donor female/recipient male	26
		Other	74

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; FK-506 = tacrolimus; HD = Hodgkin's disease; MDS = myelodysplastic syndrome; MM = multiple myeloma; MPD = myeloproliferative disorder; NHL = non-Hodgkin's lymphoma; PCL = plasma cell leukemia; Thal = thalessemia; VP16 = etoposide.
[a]ASBMT RFI 2006 Disease Risk Corresponding to CIBMTR Classifications.

Table 2 Hospital utilization during the first 100 days

	Value (range)
No. of patients admitted during preparative regimen	13
No. of patients discharged following transplant	79
Median day of admission post transplant	Day +7 (+3–69)
Median length of hospital stay	
Through day +30	12 (1–44)
Through day +100	15 (1–100)

Table 3 Engraftment, GVHD and infection

	Value (range)
Engraftment	
Primary engraftment	100%
Median time to cytopenic recovery	
ANC >500	12 days (8–20)
PLT >50	19 days (5–382)
GVHD	
Acute	
Grade II–IV	34%
Grade III–IV	13%
Chronic	56%
GVHD mortality	14%
Infections (first 100 days)	
Neutropenic fever	45%
Bacteremia	10%
CMV reactivation	29%

HSCT from an HLA-identical sibling donor for high risk (60) or standard risk (40) hematologic malignancies (Table 1). Patients received either a high-dose BU-containing (81) or TBI-based (19) preparative regimen. The stem cell source was peripheral blood (89), BM (10) or both (1). Tacrolimus plus MTX (93), CYA plus MTX (3) or tacrolimus alone (4) was administered for GVHD prophylaxis.

Hospital utilization

Hospital utilization for these 100 patients is described in Table 2. In total, 87 patients completed their preparative regimen in the outpatient setting. Five patients were admitted before starting high-dose chemotherapy due to compliance concerns (4) or medical conditions (1) and eight patients were admitted during their preparative regimen for chemotherapy-induced toxicities. A total of 79 patients were discharged to the outpatient clinic after stem cell infusion, whereas 21 patients remained hospitalized from the time of stem-cell infusion until engraftment due to chemotherapy-induced toxicities. From the time of stem cell infusion to day +30, 61 of 79 patients (77%) were readmitted to the hospital. The median day of readmission post transplant was day +7. The reasons for readmission included mucositis/pain (39%), fever (37%), nausea/vomiting (9%), acute GVHD (5%), documented infection (5%) or other causes (5%). Of the patients readmitted to the hospital, only two required direct admission to the ICU and both of these patients were eventually discharged from the hospital. Four additional patients required ICU transfer within 48 h of hospitalization, and three of these patients were safely discharged home.

From the first day of conditioning therapy to day +30 post-transplant, patients spent a median of 12 (range 1–44) days in the in-patient unit. When analyzed to day +100 post-transplant, patients spent a median of 15 (range 1–100) days in the hospital. Of note, 18 patients were treated exclusively in the outpatient setting for the first 100 days, excluding the brief planned admission for stem cell infusion.

Engraftment, GVHD and infection

Early transplant outcomes, including engraftment time, incidence of GVHD, and infection rates during the first 30 days were evaluated (Table 3). Engraftment was achieved in 100% of patients with neutrophil (ANC> 500) and plt (> 50 000) recovery occurring at a median of 12 and 19 days, respectively. Grades II–IV acute GVHD occurred in 34% of patients (Grades III–IV (14%)) and chronic GVHD occurred in 56% of patients. Although neutropenic fever occurred in 45 patients, including 10 patients with documented bacteremia, none of these patients died of sepsis or infectious death. In the first 100 days post-transplant, no documented *Aspergillus* or other mold infections were found. CMV reactivation before day +100 occurred in 29 patients but there was no early CMV disease-related mortality.

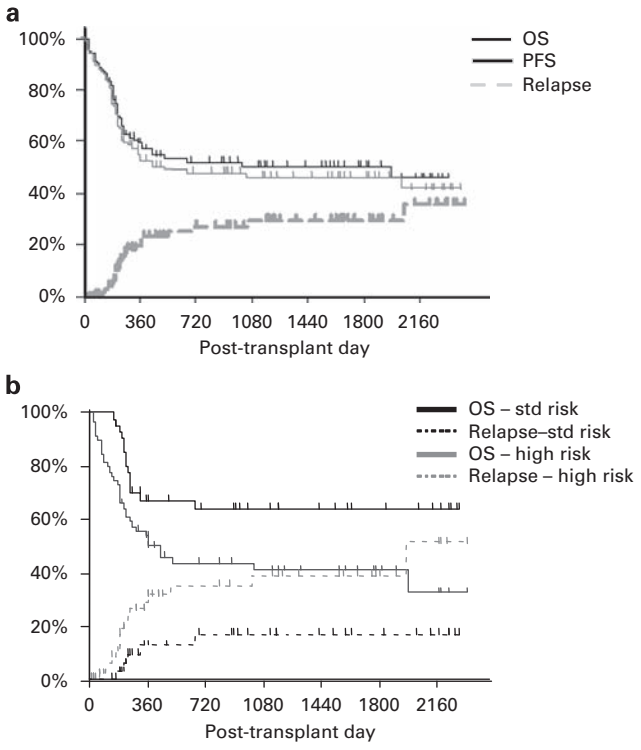

Figure 1 Kaplan–Meier analysis of (**a**) relapse, overall and progression-free survival for all patients, and (**b**) overall survival and relapse according to disease risk.

Survival, non-relapse mortality and relapse

At a median follow-up time of 3.6 years (range 0.5–6.5 years) for living patients, the estimated 4-year incidence of relapse, PFS and OS were 29, 48 and 50%, respectively (Figure 1a). Stratifying for disease risk, OS and relapse risk were 64 and 16.5%, respectively, for patients with standard risk disease and 41 and 38.5%, respectively, for patients with high-risk disease (Figure 1b). Non-relapse mortality at day 100 and 6 months was 10 and 15%, respectively. For the subset of standard risk patients ($n=40$), NRM at day 100 and 6 months was 0 and 4.9%, respectively (Table 4). The primary cause of death is outlined in Table 5. Progressive disease and GVHD were the two most common reasons for death.

Table 4 TRM and relapse

	All patients (n = 100) (%)	*Standard risk (m = 40) (%)*	*High risk (n = 60) (%)*
Non-relapse mortality 100 day	10.00	0	17.10
Non-relapse mortality 6 months	15.30	4.90	22.70
Relapse (at 5 years)	28.90	16.50	38.50

Table 5 Primary cause of death

Cause	*Patients (%)*
Progressive disease	18 (38)
GVHD	15 (31)
Organ failure	8 (17)
Infection	5 (10)
Secondary malignancy	1 (2)
Cerebral vascular disease	1 (2)

Discussion

Our study of 100 consecutive patients shows the feasibility and safety of a comprehensive outpatient treatment approach for myeloablative matched-related donor allogeneic transplant recipients. This is most clearly shown by the low early NRM seen in this patient population. Our results indicate that outpatient-based allogeneic HSCT is able to significantly reduce in-patient length of stay by more than half that expected with traditional in-patient management without causing an increase in clinical complications. Recent survey of initial hospital length of stay for allogeneic transplant patients at the US centers documented an average initial stay of 34 days, and did not include subsequent readmissions during the first 100 days after transplantation.[22]

To our knowledge, this is the first published clinical experience of a systematic outpatient management approach applied prospectively to a population of unselected allogeneic HSCT patients receiving standard myeloablative conditioning. Since the early 1990s, there have been several published reports of successful outpatient-based autologous HSCT.[7–15] The experience with outpatient management of allogeneic HSCT has been quite limited outside the context of nonmyeloablative HSCT.[16–18] The group at John Hopkins reported on an in-patient–outpatient continuum-of-care model for both autologous and allogeneic HSCT that resulted in a substantial cost savings, particularly in patients with standard risk disease, without an increase in clinical complications.[19] These patients were given the option of receiving care in the outpatient setting from the time of their preparative regimen until count recovery unless a complication arose. Of the 132 patients included in this analysis, only 17 patients (13%) received outpatient management. Of the 68 patients receiving allogeneic HSCT, only 8 patients (12%) received outpatient transplants, leaving questions regarding its generalizability. More recently, Svahn *et al*.[4] reported on their experience with outpatient allogeneic HSCT in a selected group of patients treated at a single Swedish hospital, showing that this approach translated into lower TRM and reduced costs. Outpatient treatment was provided to 36 of 179 patients (20%) receiving allogeneic HSCT. The decision to treat patients in the outpatient setting in both studies was based on patient preference, ability to meet stringent psychosocial criteria and other miscellaneous factors (for example, refusal by insurers).

In our experience, outpatient management can be performed in the vast majority of patients receiving myeloablative allogeneic HSCT. Only 5 of 100 patients were admitted prospectively to receive their high-dose preparative regimen due to compliance (4) or medical (1) concerns. In total, 87% of patients received their entire

preparative regimen in the outpatient infusion center. Almost 80% of patients were discharged from the hospital after their brief planned admission for stem cell infusion and were followed up daily in the outpatient infusion center. Although the majority of patients are readmitted to the hospital at a median of day +7 post-transplant, approximately one-fifth of patients are treated exclusively in the outpatient setting, excluding the brief planned admission for stem cell infusion.

This study adds to the growing literature regarding the safety of outpatient management of patients after high-dose chemoradiotherapy. Earlier concerns have included the increased risks of mucosal toxicity, infections, septic shock and organ failure associated with high-dose conditioning regimens, and the possibility of worse outcomes if patients are not monitored closely in the hospital. Outpatient management also runs contrary to commonly held beliefs regarding the importance of protective isolation and air handling techniques, although there remains considerable controversy regarding its importance.[23] Despite outpatient management, we noted a low incidence of serious infections. Although patients spent considerable time in their homes during the pancytopenic phase, outside of protective isolation, we documented no increase in the incidence of invasive *Aspergillus* or other mold infections. A total of 45 patients required readmission to the hospital secondary to neutropenic fever (10 patients with documented bacteremia), but none of these patients died of sepsis or infectious death.

The low incidence of infectious complications and non-relapse mortality seen in this study, despite myeloablative conditioning, may in part be the result of a strict adherence to supportive care algorithms. Patients were evaluated daily by a mid-level practitioner, pharmacist and physician after hospital discharge. Compliance with antimicrobial prophylaxis, immunosuppressive therapy and other medications was reinforced using home medicine administration records. Patients were admitted promptly for complications requiring in-patient management, such as neutropenic fever.

Although a formal quality-of-life survey was not included as part of the analysis, it was evident from satisfaction questionnaires that patients universally valued the treatment delivered in the outpatient setting. In fact, few patients requested to receive more traditional in-patient management, usually due to transportation or caregiver concerns. In the autologous HSCT setting, outpatient management has been associated with improved patient satisfaction and quality-of-life.[9,11] We expect to see similar outcomes in allogeneic HSCT and currently use formal quality-of-life questionnaires to test this hypothesis.

An outpatient management strategy significantly reduces hospitalization, which has an immediate benefit in reducing the pressure on available beds. Although a potential for cost savings exists, it is more difficult to show, as much of the in-patient cost reduction is simply shifted to the outpatient setting.[19] However, several studies have documented a 25–45% decrease in total medical charges associated with an outpatient management strategy[4,9,14,19] that could translate into substantial savings if applied to a significant proportion of more than 15 000 patients receiving HSCT in North America each year (data from the Center for International Blood and Marrow Transplant Research).

In summary, this study confirms that outpatient myeloablative allogeneic HSCT is feasible with regard to outpatient delivery of high-dose conditioning therapy and expectant management of post-transplant complications. Such a strategy can be safely applied the vast majority of patients with low treatment-related morbidity and mortality, and clinical outcomes comparable to that expected with traditional in-patient management. In addition to a dramatic reduction in hospital utilization, potential exists for cost reduction and improvements in quality-of-life.

Conflict of interest

The authors declare no conflict of interest.

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