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Outcomes of Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation Performed in the Inpatient versus Outpatient Setting

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Allogeneic hematopoietic cell transplantation (allo-HCT) with reduced-intensity conditioning (RIC) is commonly performed as an inpatient procedure. The feasibility and outcomes of RIC allo-HCT in the outpatient setting is not known. We performed a single-center retrospective cohort study of patients aged ≥ 18 years with hematologic malignancies who underwent RIC allo-HCT either in the inpatient or outpatient setting. Donor types included HLA-matched sibling and well-matched unrelated donors. The objectives were to compare the survival, complications, charges, and incidences of relapse, nonrelapse mortality (NRM), and acute and chronic graft-versus-host disease (GVHD) between the 2 groups. Between 2014 and 2017, 151 eligible patients were included, with 116 undergoing RIC allo-HCT in the inpatient setting and 35 patients undergoing RIC allo-HCT in the outpatient setting. Baseline characteristics were comparable between the 2 groups except for a higher proportion of patients with myeloma in the outpatient cohort (inpatient 15.5% versus outpatient 37.1%). The cumulative incidence of grades II to IV acute GVHD (inpatient 25.2% versus outpatient 25.7%), grades III to IV acute GVHD (inpatient 10.4% versus outpatient 8.5%), chronic GVHD (inpatient 38.3% versus outpatient 51.6%), NRM at 1 year (inpatient 10.8% versus outpatient 3.2%), and relapse (inpatient 24.8% versus outpatient 33.2%) did not significantly differ between the 2 cohorts. One-year progression-free survival (inpatient 64.4% versus outpatient 63.6%, P = .39) and overall survival (inpatient 73.8% versus outpatient 82.8%, P = .93) were also not significantly different between the 2 groups. The proportion of patients who developed neutropenic fever (inpatient 25.8% versus outpatient 8.5%, P = .03) and mucositis (inpatient 50.8% versus outpatient 8.5%, $P < .001$) and who required total parenteral nutrition (inpatient 20.6% versus outpatient 5.7%, P = .04) were more frequent in the inpatient cohort. About 51.5% of the outpatient cohort never required hospital admission in the first 100 days. Outpatient HCT resulted in significantly lower charges than inpatient HCT in the first 100 days (median charges: inpatient $339,621 versus outpatient $247,334; $P < .001$). On multivariate analysis the site of the HCT (outpatient versus inpatient) was not a significant predictor of either overall or progression-free survival. Outpatient RIC allo-HCT is feasible and safe with daily outpatient evaluation and aggressive supportive care resulting in outcomes comparable with those who received the transplant in the inpatient setting.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a commonly used therapeutic option for patients with advanced and/or high-risk hematologic malignancies [1]. In United States the current report from the Center for International Blood and Marrow Transplant Research estimates that about 8500 allo-HCTs were performed in 2016, with a steady increase in the use of reduced-intensity conditioning (RIC) regimens, in parallel with increased application of this procedure in patients ages 60 or older [1]. Because of the intensity of the procedure and potential complications, allo-HCT is generally performed in the inpatient setting. Importantly, allo-HCT is a

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resource-intensive procedure with an average national cost ranging over 267,000 U.S. dollars [2,3].

Conducting HCT in the outpatient setting is an attractive option. It has several potential advantages such as patient independence, lesser utilization of hospital inpatient resources, decreased risk of nosocomial infections, and possibly reduced costs. However, the current literature comparing the outcomes of outpatient versus inpatient HCT is mostly in the setting of autologous transplants and generally supports outpatient HCT's feasibility and favorable impact on cost of care [4–7]. Consequently, data are scarce regarding the safety, feasibility, outcomes, and cost impact of outpatient RIC allo-HCT, relative to the conventional inpatient model. We report a retrospective single-center study evaluating the feasibility and outcomes of RIC allo-HCT performed in the outpatient setting compared with a contemporaneous cohort of patients who underwent the same intensity procedure in the inpatient setting.

METHODS

We performed a single-center, retrospective study of consecutive patients who underwent a RIC allo-HCT for hematologic malignancies from either HLA-matched related or unrelated donors at our center between January 2014 and January 2017. The patient population was divided into inpatient HCT versus outpatient HCT cohorts. Data were obtained by chart review and from a prospectively maintained institutional transplant database. Outpatient RIC allo-HCT was offered to patients meeting all the following criteria: planned use of a RIC regimen, undergoing a matched related or unrelated donor HCT, either permanent residence within 45 minutes of the transplant center or ability to secure temporary housing close (with 45 minutes) to the center, and patient willingness to undergo outpatient HCT. The study was approved by the Institutional Review Board of the Medical College of Wisconsin.

Procedure

Patients undergoing outpatient HCT received their care in an outpatient infusion center (day hospital). During outpatient HCT the day hospital was equipped to deliver all aspects of transplantation care including administration of conditioning regimen, stem cell infusion, and post-transplant monitoring. The day hospital is designed to administer intravenous antibiotics, chemotherapy drugs, blood products, other types of infusions, or advanced services that might otherwise require hospitalization. Patients were required to have daily visits with laboratory monitoring (comprehensive metabolic panel, complete blood count, viral monitoring, and immunosuppressive drug level monitoring) and supportive care (including central line care, fluid balance monitoring, transfusions, etc.) from the start of the conditioning regimen until hematopoietic recovery. Patients were evaluated daily by a bone marrow transplant physician and/or a mid-level provider and transplant nursing staff. During work hours physician coverage was provided by the patient's primary transplant physician and after hours by the on-call bone marrow transplant attending physicians. The day hospital was also fully functional on weekends and holidays. Outpatient transplant recipients developing significant complications precluding outpatient care (eg, development of neutropenic fevers, persistent diarrhea, severe mucositis, intractable nausea/vomiting leading to inadequate oral intake, hemodynamic instability, respiratory distress, sepsis, etc.) were transferred to the inpatient transplantation unit. The time spent by individual patients in the outpatient infusion rooms during daily visits was not systemically captured, although at our center it typically varied between 7 and 10 hours depending on the need for supportive care. In the inpatient cohort, patients were admitted from the start of the conditioning regimen and kept inpatient until hematopoietic recovery and resolution of any complications that would require continued inpatient stay.

Prophylaxis and Supportive Care

All transplant recipients underwent either a central venous catheter insertion or peripherally inserted central catheter placement. Patients in both inpatient and outpatient settings received similar supportive care including daily line care, antiemetics, intravenous hydration (as appropriate), electrolyte replacement, viral monitoring, and transfusion support. Prophylactic antimicrobials in both cohorts included fluconazole for antifungal prophylaxis, acyclovir for antiviral prophylaxis, and trimethoprim/sulfamethoxazole for *Pneumocystis* prophylaxis. With regards to antibacterial prophylaxis, inpatient recipients received fluoroquinolones during neutropenia, whereas outpatients received fluoroquinolones starting on day +1, with intravenous ertapenem added during neutrophil nadir (ie, absolute neutrophil count $\leq 500/\mu L$). In both cohorts platelet transfusion was given when the platelet count was $<10{,}000/\mu L$ in the absence of any other medical indications that would require a higher platelet count. Similarly, in both cohorts packed RBC transfusion was given to maintain a hemoglobin > 7 g/dL in the absence of any other medical indications that would require a higher hemoglobin threshold.

Statistical Analysis

The primary objective was to compare the 1-year progression-free survival (PFS) and overall survival (OS) between patients who underwent RIC allo-HCT in the inpatient versus outpatient setting. Secondary objectives included comparison of the cumulative incidence of relapse, nonrelapse mortality (NRM), acute and chronic graft-versus-host disease (GVHD), complications within the first 100 days of transplantation, and charges incurred from the initiation of conditioning through day +100 between patients who underwent RIC allo-HCT in the inpatient versus outpatient setting.

Descriptive statistics were used to analyze baseline characteristics. Continuous variables were compared using nonparametric Wilcoxon test and categorical variables using the chi-square or Fisher's exact test. Because the outpatient and inpatient cohorts were well balanced with no major significant differences in their baseline characteristics, further case matching between the cohorts was not needed.

Primary hematologic malignancy was broadly stratified into 4 groups: acute leukemia (which included acute myeloid leukemia, acute lymphoblastic leukemia), lymphoma (Hodgkin lymphoma, non-Hodgkin lymphoma), multiple myeloma, and myelodysplastic syndrome/myeloproliferative neoplasm. Disease risk before transplant was assessed according to the Disease Risk Index (DRI) [8]. Comorbidities were scored according to the HCT-specific comorbidity index (HCT-CI) [9]. Performance status was reported using the Karnofsky performance score (KPS). Acute and chronic GVHD were assessed using consensus criteria [10,11]. RIC regimen was assigned according to consensus recommendation [12].

Time to neutrophil engraftment was defined as the first day of an absolute neutrophil count $> 500/\mu L$ for 3 consecutive days. Time to platelet recovery was defined as the first day of platelet count $> 20\,000/\mu L$ without need for transfusion in the preceding 7 days. Readmission in the outpatient cohort was defined by any inpatient admission after the day of hematopoietic cell infusion. In the inpatient setting, readmission was defined by any subsequent admission after discharge from the original inpatient transplant-related admission.

OS was defined from the time of transplant until death from any cause. Surviving patients were censored at last follow-up. PFS was defined from the time of transplant until disease progression or relapse or death. NRM was defined as death occurring after transplant, not due to disease progression, with relapse as a competing event. Kaplan-Meier methods and log-rank tests were used to compare OS and PFS probabilities, and cumulative incidence functions were used for NRM, relapse rate, and acute and chronic GVHD. Multivariate analysis of OS and PFS was performed using the Cox proportional hazard regression method. Readmission rates were compared for both cohorts using descriptive statistics. HCT charge estimates were calculated from the date of initiation of the conditioning regimen through day +100, using hospital charges on all individual patients included in this report, and this included outpatients who were never admitted until day +100. All statistical analyses were performed with a 2-sided significant $P < .05$ using SAS statistical software (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

A total of 151 patients were included in the analysis, with 116 patients undergoing transplant in the inpatient setting and 35 in the outpatient setting. The median patient age was comparable between the 2 groups (inpatient 65 years versus outpatient 63 years, $P = .33$). Both cohorts had predominantly male (inpatient 62.9% versus outpatient 60%) and white patients (inpatient 95.6% versus outpatient 97.1%) with no significant differences based on gender or race. The outpatient cohort had a significantly higher proportion of myeloma patients (inpatient 15.5% versus outpatient 37.1%) and a lower proportion of patients with myelodysplastic syndrome/myeloproliferative neoplasm (inpatient 35.3% versus outpatient 17.1%, $P = .03$). Of note, the 2 cohorts did not significantly differ in terms of factors such as DRI, HCT-CI, KPS, donor type, graft source, conditioning regimen, GVHD prophylaxis, donor–recipient ABO match, gender match, and cytomegalovirus match, as described in Table 1. The median interval between diagnosis and transplant was not significantly different between the 2 groups (inpatient 290 days

Table 1
Baseline Characteristics

Variable	Inpatient (n = 116)	Outpatient (n = 35)	*P*
Median age, yr (range)	65 (25-77)	63 (27-75)	.33
Gender			.84
Male	73 (62.9%)	21 (60%)	
Female	43 (37.1%)	14 (40%)	
Race			.61
White	111 (95.6%)	34 (97.1%)	
Black	1 (.8%)	1 (2.8%)	
Asian	3 (2.5%)	0 (0%)	
Hispanic	1 (.8%)	0 (0%)	
Disease			.03*
Acute leukemia	37 (31.9%)	10 (28.5%)	
Lymphoma	20 (17.2%)	6 (17.1%)	
Myeloma	18 (15.5%)	13(37.1%)	
MDS/MPN	41 (35.3%)	6 (17.1%)	
DRI			.72
Low	13 (11.2%)	2 (5.7%)	
Intermediate	83 (72.8%)	28 (80%)	
High	20 (16.0%)	5 (14.3%)	
HCT-CI			.67
0	26 (22.5%)	5 (14.4%)	
1	28 (24.1%)	11 (31.4%)	
2	25 (21.5%)	9 (25.7%)	
3+	37 (31.9%)	10 (28.5%)	
KPS			1.00
90-100	35 (30.2%)	12 (34.3%)	
<90	81 (69.8%)	23 (65.7%)	
Donor type			.56
Matched related	55 (47.4%)	14 (40%)	
Matched unrelated	61 (52.5%)	21 (60%)	
Stem cell			1.00
Peripheral blood	112 (96.5%)	34 (97.2%)	
Bone marrow	4 (3.5%)	1 (2.8%)	
RIC regimen			.09
Fludarabine/busulfan	83 (72%)	19 (54.3%)	
Fludarabine/melphalan	33 (28%)	16 (45.7%)	
Donor–recipient gender			.47
Male–male	37 (31.9%)	15 (42.8%)	
Male–female	25 (21.5%)	9 (25.7%)	
Female–male	35 (30.3%)	7 (20.1%)	
Female–female	19 (16.3%)	4 (11.4%)	
Donor–recipient cytomegalovirus			0.81
Positive–positive	23 (19.8%)	6 (17.2%)	
Positive–negative	18 (15.6%)	8 (22.8%)	
Negative–positive	36 (31.0%)	10 (28.5%)	
Negative–negative	39 (33.6%)	11 (31.5%)	
Donor–recipient ABO			.26
Matched	66 (56.9%)	18(51.5%)	
Major mismatch	19(16.4%)	11(31.5%)	
Minor mismatch	25(21.5%)	5(14.2%)	
Bidirectional	6 (5.2%)	1 (2.8%)	
Median baseline absolute neutrophil count, $\times 10^3/\mu L$ (range)	3.8 (.1-15.8)	2.2 (.3-6.9)	<.001*
Median baseline platelet count, $\times 10^3/\mu L$ (range)	120 (9-618)	133.5 (23-360)	.39
Median interval between diagnosis and transplant, days (range)	290 (75-9046)	297 (117-3530)	.34

* $P < .05$, significant.

versus outpatient 297 days, $P = .34$). The median baseline absolute neutrophil count was significantly lower in the outpatient cohort (inpatient $3.8 \times 10^3/\mu L$ versus outpatient $2.2 \times 10^3/\mu L$, $P < .001$). The median baseline platelet count was not significantly different between the 2 groups (inpatient $120 \times 10^3/\mu L$ versus outpatient $133.5 \times 10^3/\mu L$, $P = .39$). All patients received tacrolimus and methotrexate for GVHD prophylaxis.

Transplant Outcomes

The median duration of follow-up of survivors in both cohorts was 17 months. The median time to neutrophil recovery was 17 days in the inpatient cohort and 16 days in the outpatient cohort ($P = .39$). The median time to platelet recovery was 18 days in both cohorts ($P = .31$). There was no significant difference in the cumulative incidence of grades II to IV acute GVHD at day 100 (inpatient 19.1% versus outpatient 25.7%) and day 180 (inpatient 25.2% versus outpatient 25.7%, $P = .78$) in the 2 groups (Figure 1A). Similarly, the cumulative incidence of grades III to IV acute GVHD at day 100 (inpatient 6.9% versus outpatient 8.5%) and day 180 (inpatient 10.4% versus outpatient 8.5%, $P = .40$) were not significantly different between the 2 groups. The cumulative incidence of chronic GVHD (inpatient 38.3% versus outpatient 51.6%, $P = .11$) was also comparable between both groups (Figure 1B). The NRM at 1 year (inpatient 10.8% versus outpatient 3.2%, $P = .17$) was not significantly different between both cohorts (Figure 1C). The cumulative incidence of relapse at 1 year was 24.8% in the inpatient and 33.2% in the outpatient cohorts ($P = .37$) (Figure 1D). PFS at 1 year was 64.4% in the inpatient and 63.6% in the outpatient groups ($P = .39$) (Figure 1E), whereas OS at 1 year was 73.8% and 82.8% in the same corresponding cohorts ($P = .93$) (Figure 1F).

Complications and Readmissions within the First 100 Days

The proportion of patients who developed complications such as viral reactivations, bacteremia, invasive fungal infection, and *Clostridium difficile* infections was not significantly different between both cohorts as illustrated in Table 2. Similarly, both groups had a comparable proportion of patients who had complications such as acute renal dysfunction, requirement for hemodialysis, mechanical ventilation, and intensive care unit transfers (Table 2). The inpatient cohort had a higher proportion of patients who had mucositis (inpatient 50.8% versus outpatient 8.5%, $P < .001$), although the grades of mucositis were not consistently documented in the charts. Similarly, the inpatient group also had a higher proportion of patients who developed neutropenic fevers (inpatient 25.8% versus outpatient 8.5%, $P = .03$) and who required total parenteral nutrition (inpatient 20.6% versus outpatient 5.7%, $P = .04$). Six patients (17.1%) from the outpatient cohort required inpatient admission before neutrophil recovery. The reasons for admissions before neutrophil recovery include neutropenic fever (n = 1), hypotension/acute kidney injury (n = 1), seizure (n = 1), tacrolimus toxicity (n = 1), transaminitis (n = 1), and mucositis (n = 1). The rate of hospital readmissions during the first 100 days (ie, readmission of an inpatient after discharge from the index hospitalization or any hospital admission of the outpatient cohort patients during 100 days post-HCT) was not significantly different between the 2 groups (Table 2). Among the outpatient cohort, 51.5% of patients never required hospitalization within the first 100 days.

Multivariate Analysis

On multivariate analysis, disease type (lymphoma: hazard ratio [HR], .30; 95% confidence interval [CI], .09 to .94; $P = .03$) and DRI (intermediate: HR, .27; 95% CI, .14 to .52; $P < .01$) were found to be significant predictors of mortality risk. The DRI (intermediate: HR, .26; 95% CI, .13 to .53; $P = .002$; low: HR, .25; 95% CI, .08 to .91; $P = .03$) was also found to be a significant predictor of PFS. Site of the HCT (outpatient versus inpatient) was not a significant predictor of OS or PFS (Tables 3 and 4).

Costs

During the first 100 days post-HCT total charges (measure of cost in the current analysis) of the outpatient cohort (median, \$247,334; range, \$152,080.37 to \$1,137,124.74) were significantly lower compared with that for the inpatient cohort

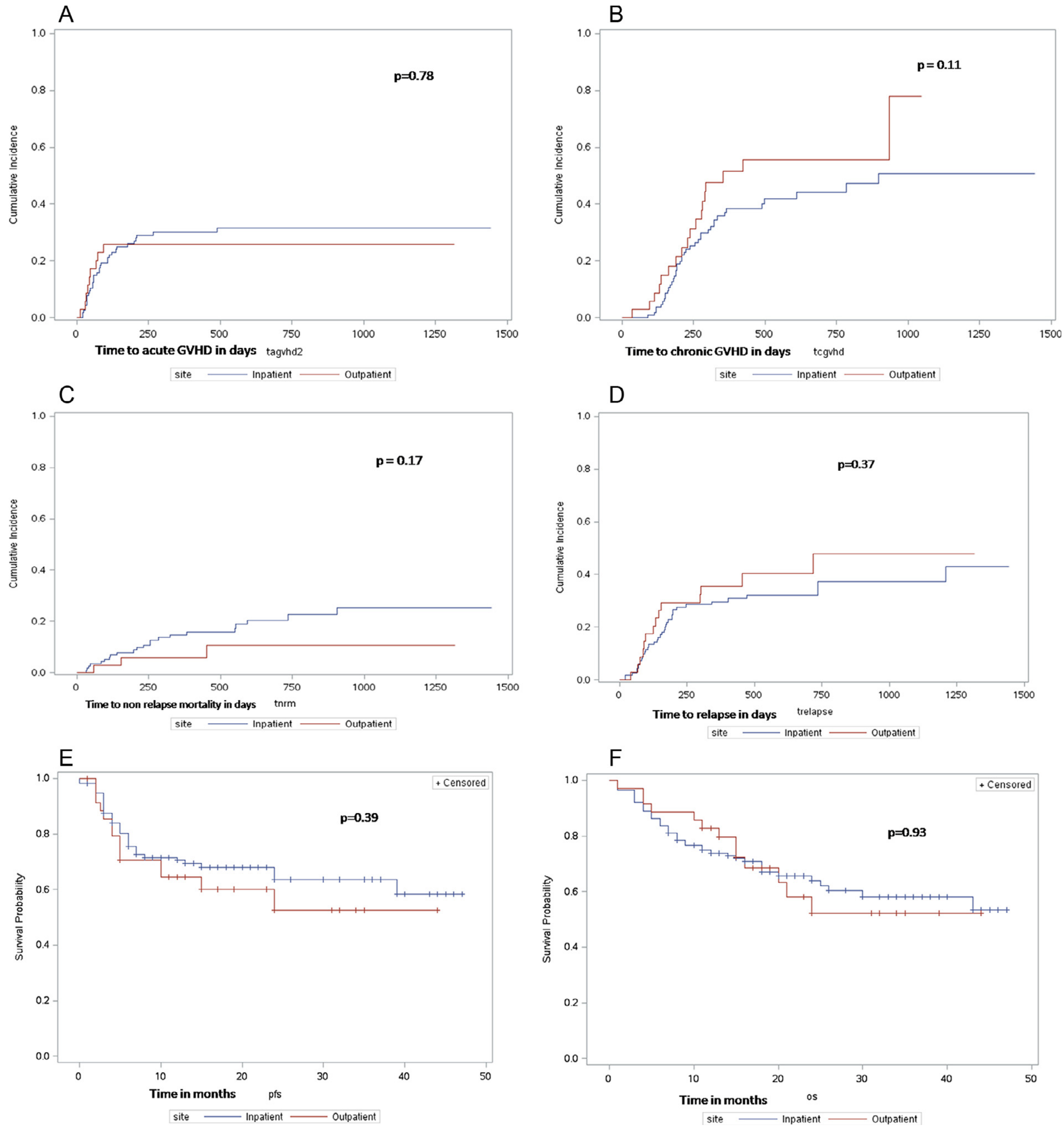

Figure 1. (A) Cumulative incidence of acute GVHD grades II to IV. (B) Cumulative incidence of chronic GVHD. (C) Cumulative incidence of NRM. (D) Cumulative incidence of relapse. (E) Progression-free survival. (F) Overall survival.

(median, $339,621; range, $212,666.20 to $1,280,317.19; $P < .001$). Among those in the outpatient cohort, patients who were readmitted within the first 100 days had significantly higher charges (median, $316,262; range, $221,291 to $1,137,124) than those who never required readmission (median, $208,858; range, $152,080 to $322,225; $P < .001$). A comparison of the charges in the inpatient cohort (n = 116) versus those in the outpatient cohort who were readmitted (n = 17) showed no statistically significant difference between the cost (inpatient versus outpatient: median $339,621 versus $316,262; $P = .34$).

DISCUSSION

In the current study we describe the feasibility and safety of RIC allo-HCT performed in the outpatient setting with several important observations. First, we found that the outcomes such as survival, relapse, NRM, and GVHD were comparable in carefully selected patients undergoing outpatient allo-HCT relative to a contemporaneous inpatient cohort. Second, hospital resource utilization in terms of intensive care unit use, mechanical ventilation, renal replacement therapy, and so on was not significantly different between the 2 cohorts. Third, the risk of neutropenic fever was lower in the outpatient cohort, and, finally, the outpatient RIC allo-HCT may have a favorable impact on cost of transplantation (when using hospital charges as a surrogate marker for cost).

In the current era of transplantation and escalating healthcare costs, curtailing procedure-related costs and resource utilization is a priority among many transplantation centers. An

Table 2
Complications within First 100 Days

Complication	Inpatient (n = 116)	Outpatient (n = 35)	P
Bacterial infections	28 (24.1%)	5 (14.2%)	.25
Viral infections			
Cytomegalovirus reactivation	16 (13.7%)	6 (17.1%)	.59
Epstein-Barr virus infection	1 (.8%)	0 (0%)	1.00
BK virus hemorrhagic cystitis	5 (4.3%)	0 (0%)	.59
Invasive fungal infections	1 (.8%)	0 (0%)	1.00
Clostridium difficile infection	18 (15.5%)	3 (8.5%)	.40
Transfers to medical intensive care units	15 (12.9%)	3 (8.5%)	.76
Mechanical ventilation	11 (9.4%)	1 (2.8%)	.29
Renal replacement therapy	5 (4.3%)	1 (2.8%)	1.00
Acute renal dysfunction[†]	55 (47.4%)	15 (42.8%)	.70
Total parenteral nutrition	24 (20.6%)	2 (5.7%)	.04*
Mucositis[‡]	59 (50.8%)	3 (8.5%)	<.001*
Neutropenic fever	30 (25.8%)	3 (8.5%)	.03*
Hospital Readmissions within 100 days of HCT[§]	40 (34.3%)	17 (48.5%)	.16

* $P < .05$, significant.
† Renal dysfunction: increase in serum creatinine ≥ .3 mg/dL in 48 hours.
‡ Mucositis grade not available.
§ Defined as readmission of an inpatient HCT patient after being discharged from the index hospitalization or any hospital admission of the outpatient cohort patients during 100 days post-HCT.

Table 3
Multivariate Analysis of OS

Factor	HR	95% CI	P
Site			
Inpatient	Ref.	.54-2.03	.88
Outpatient	1.05		
Age	.97	.94-1.00	.07
Gender			
Male	Ref.	.67-2.14	.53
Female	1.20		
Disease			
Acute leukemia	Ref.	.39-1.51	.45
MDS/MPN	.77	.11-1.06	.06
Myeloma	.34	.09-.94	.03*
Lymphoma	.30		
DRI			
High	Ref.	.14-.52	<.01*
Intermediate	.27	.09-1.59	.19
Low	.29		
HCT-CI			
0	Ref.	.29-1.72	.44
1	.71	.60-3.38	.41
2	1.42	.41-2.10	.87
3+	.93		
KPS			
90-100	Ref.	.53-2.04	.90
<90	1.04		
Donor type			
Matched related	Ref.	.59-2.09	.74
Matched unrelated	1.11		
Stem cell			
Peripheral blood	Ref.	.09-2.86	.44
Bone marrow	.51		
Conditioning regimen			
Fludarabine/busulfan	Ref.	.63-3.42	.36
Fludarabine/melphalan	1.47		

MDS/MPN indicates myelodysplastic syndrome/myeloproliferative neoplasm.
* $P < .05$, significant.

Table 4
Multivariate Analysis of PFS

Factor	HR	95% CI	P
Site			
Inpatient	Ref.	.64-2.51	.48
Outpatient	1.27		
Age	1.02	.99-1.06	.10
Gender			
Male	Ref.	.76-2.62	.26
Female	1.41		
Disease			
Acute leukemia	Ref.	.23-1.17	.11
MDS/MPN	.52	.31-3.34	.97
Myeloma	1.02	.73-4.40	.19
Lymphoma	1.80		
DRI			
High	Ref.	.13-.53	.002*
Intermediate	.26	.08-.91	.03*
Low	.25		
HCT-CI			
0	Ref.	.32-1.85	.57
1	.78	.39-2.42	.89
2	.94	.20-1.09	.08
3+	.97		
KPS			
90-100	Ref.	.84-3.39	.13
<90	1.69		
Donor type			
Matched related	Ref.	.31-1.12	.11
Matched unrelated	.59		
Stem cell			
Peripheral blood	Ref.	.54-15.21	.21
Bone marrow	2.87		
Conditioning regimen			
Fludarabine/busulfan	Ref.	.42-2.82	.84
Fludarabine/melphalan	1.09		

* $P < .05$, significant.

outpatient-based HCT offers several advantages. In the literature various outpatient models of autologous HCT have been described [4–7]. One is the early discharge model in which high-dose chemotherapy and stem cell infusion are performed in the inpatient setting, after which patients are discharged to an outpatient care model [4]. The second is the delayed admission approach in which patients receive conditioning regimen and stem cell infusion as outpatients and are admitted after entering the aplastic phase of the transplant [5]. The third model is the total outpatient approach where the conditioning regimen, stem cell infusion, and post-HCT monitoring are all carried out in the outpatient setting [6,7]. Although each method has its merits and demerits and is guided by institutional policies, the total outpatient approach is likely to provide the advantage of curtailing inpatient stay–related expenses in a subset of patients who never require hospitalization within the first 100 days of allo-HCT.

A few published reports have described the outcomes of allo-HCT performed in the outpatient setting using myeloablative conditioning. A nonrandomized prospective cohort study by Rizzo et al. [13] evaluated the outcomes of 132 consecutive patients who underwent HCT either in the inpatient or outpatient setting. They found that outpatient HCT resulted in substantial cost savings without adverse effects in patients who did not have a high risk of treatment failure. However, the number of patients who underwent outpatient allo-HCT in this study was low (n = 8) and was not limited to RIC patients. Similar studies on outpatient allo-HCT have also been described from US studies, although no cost data have been reported [14,15].

Our present study describes the short-term outcomes and complications of RIC allo-HCT in the first 100 days, in addition to the traditional outcomes such as survival, relapse, and GVHD. Both cohorts in the present study were comparable in terms of various patient-related, disease-related, and transplant-related characteristics at baseline, except for more patients with myeloma undergoing outpatient RIC allo-HCT and a higher proportion of myelodysplastic syndrome/myeloproliferative neoplasm patients undergoing the procedure in the inpatient setting. However, although different diseases were included in our study, the DRI was comparable between the outpatient and inpatient cohorts, meaning the cohorts were balanced in terms of their risk of relapse. Additionally, predictors of patients' ability to tolerate the procedure such as performance status and HCT-CI were not significantly different between the 2 groups, ensuring a reasonable comparison. We found that the duration of hematopoietic recovery, incidence of infectious complications, intensive care unit transfer, renal dysfunction, and hemodialysis were not significantly different between both cohorts, whereas the incidence of neutropenic fever and mucositis was higher in the inpatient cohort. Unfortunately, the grade of mucositis was not uniformly reported in patient charts or captured in our HCT database. However, the use of total parenteral nutrition (a potential surrogate of mucositis severity) was also significantly higher in the inpatient cohort. Because subjects in the outpatient cohort were assessed daily by a bone marrow transplant provider (with daily electronic progress notes documented), differences in the frequency of assessment is not a likely explanation of the difference in the rates of mucositis. Factors such as limited sample size in the outpatient cohort and differences in pretransplant baseline characteristics that were not captured in our study could have affected these outcomes and should be explored in future studies. The differences in the incidence of neutropenic fever could be from the exposure to nosocomial pathogens in the inpatient cohort. It also plausible that the gut microbiome of hospitalized patients is different from outpatients, resulting in a differential risk of infection [16,17]. The use of ertapenem prophylaxis in the outpatient cohort could also be responsible for fewer events. Additional factors influencing the differences in neutropenic fever include periodic monitoring of vital signs including temperature, which is checked more frequently by inpatient nursing staff compared with patient's self-reported temperature in the outpatient setting. Similarly, total parenteral nutrition is likely be used frequently in the inpatient setting where calorie count monitoring and the ease of continuous administration are available. We did not monitor calorie counts in the outpatient transplant cohort. Finally, lesser mucositis, total parenteral nutrition, and neutropenic fever could also be explained by careful selection of patients by transplant physicians that are not always reflected in performance status and HCT-CI.

Because HCT is a resource-intensive treatment modality, the cost of hospitalization contributes to a significant proportion of the overall procedure cost [18,19]. It has been previously reported that allo-HCT using RIC resulted in lower overall cost and fewer median hospital days within the first year of HCT as compared with myeloablative conditioning [20,21]. In a study by Khera et al. [22] the cost of RIC allo-HCT in the first 100 days was found to be significantly influenced by disease and donor type, with transplant for lymphoma, myeloma. and those from matched related donors associated with lower cost. In our present study we found that outpatient RIC allo-HCT resulted in substantial cost savings within the first 100 days of transplant compared with the inpatient cohort. Additionally, about 50% of patients in the outpatient cohort never required hospitalization through day +100, similar to other reports [23]. It is important to understand the difference between cost and charges in this setting. Costs reflect the actual resources used to deliver a service, although it is difficult to capture in retrospective studies. Most prior studies in transplant economics have reported charges similar to our study, and this approach has several limitations [24]. Charges are not standardized or consistent across different hospital systems. Additionally, hospital charges do not reflect third-payer reimbursement and may not be applicable to hospitals with a different payer mix than ours (Medicare versus Medicaid versus self-pay versus private insurance).

Other limitations of our study include its retrospective design, smaller sample size, single-center data, and lack of information on patient quality of life and how it was influenced by the transplant setting. The smaller number of patients in the outpatient cohort might have hidden some differences in the outcomes of interest, although we tried to carefully take this into account in our analyses. It is possible that some degree of selection bias occurred, with more fit patients included in the outpatient cohort based on the physicians' assessment, even though the baseline characteristics in terms of KPS and HCT-CI were well balanced between the 2 groups. We do not know if the 2 cohorts were comparable in terms of their healthcare literacy or socioeconomic status. There is also a lack of standardized criteria available in literature that could guide clinicians and patients in deciding whether the transplant could be performed in the inpatient versus outpatient setting. Additionally, information on factors such as patient motivation and education, which could influence the transplant outcomes, were not available in the present study. Overall, our results provide preliminary information that outpatient-based RIC allo-HCT is feasible and safe when compared with those who undergo the same procedure as inpatients, although prospective randomized clinical trials would be needed to the definitively confirm the results of this approach. The center's resources also play an important role in the success of outpatient transplants such as the availability of experienced personnel and accessibility even during holidays and weekends.

In conclusion, an outpatient-based RIC allo-HCT program is feasible and safe in select patients and may be associated with lower healthcare costs, although many factors such as center experience, proximity to home/lodging, reliable and available caregiver, and cost to patient determine this choice. Our findings suggest that a RIC allo-HCT can be performed in a carefully selected patient population completely in the outpatient setting. It is reasonable to foresee an increase in this approach over time to reduce the procedure-related cost and improve patient comfort, thereby reserving inpatient RIC allo-HCTs for patients who are at higher risk of transplant-related complications. Development of novel standardized tools to guide appropriate patient selection for outpatient allo-HCT would be critical in future studies so that this approach can be widely adopted by other centers.

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