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Similar Risks for Chronic Kidney Disease in Long-Term Survivors of Myeloablative and Reduced-Intensity Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

Chronic kidney disease (CKD) in recipients of myeloablative (MA) allogeneic hematopoietic cell transplantation (HCT) has been well characterized. However, the risk of CKD after HCT using reduced-intensity conditioning (RIC) is not well known. We compared the incidence of CKD by conditioning regimen in 221 allogeneic HCT recipients (MA = 117, RIC = 104) who had survived for ≥1 year post-HCT and had no history of CKD pretransplant. CKD was defined as glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 months anytime after 180 days post-HCT. The median follow-up was 28 months (range: 12-75) for MA and 25 months (range: 12-67) for the RIC group. The 3-year cumulative incidence rate of CKD was 28% (95% confidence intervals [CI], 19%-36%) in MA and 29% (95% CI, 20%-38%) in the RIC group (P = .44). In multivariate analysis, conditioning regimen intensity had no impact on the risk of developing CKD (relative risk [RR] for MA 1.50 [95% CI, 0.78-2.89] versus the RIC regimen). Factors independently associated with an increased risk of CKD were older age at transplant, acute graft-versus-host disease, cyclosporine use for >6 months, and acute kidney injury in the early posttransplant period. CKD is frequent in long-term adult allogeneic HCT survivors, but RIC is associated with similar risks as MA conditioning. Continuous monitoring of renal function is necessary in allogeneic HCT survivors, and studies exploring prevention strategies are needed.

KEY WORDS

Allogeneic hematopoietic cell transplantation • Myeloablative conditioning regimen • Reduced-intensity conditioning regimen • Chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) affects 15%-40% of adult survivors of myeloablative (MA) allogeneic hematopoietic cell transplantation (HCT) [1-4]. Previous reports have described multiple clinical CKD syndromes in long-term survivors of MA HCT including progressive acute kidney injury (AKI) [1,5], nephrotic syndrome [6], and renal failure secondary to thrombotic microangiopathy [7]. Total body irradiation (TBI) and preparative regimen chemotherapy, graft-versus-host disease (GVHD), and use of calcineurin inhibitors have been implicated as risk factors for CKD [1,2,8-10]. Allogeneic HCT using reduced-intensity conditioning (RIC), which utilizes lower doses of chemotherapy with or without TBI, is being increasingly used for patients who cannot tolerate the toxicities of an MA regimen [11]. RIC regimens have been reported to be associated with lower treatment-related mortality, and may have lower morbidity compared to MA regimens [12]. However, the incidence and risk factors of CKD in survivors of RIC HCT have not been well described. We conducted a retrospective cohort study of long-term adult allogeneic HCT survivors to compare the incidence and risk factors of CKD after transplantation using RIC and MA regimens.

METHODS

Patient Population

Consecutive patients who underwent an allogeneic HCT using either MA or RIC regimens between

January 2000 and 2005 at the University of Minnesota were included in this study if: (1) they were ≥18 years of age at the time of HCT, (2) had survived at least 1 year posttransplant, and (3) had normal renal function at the time of HCT. Patients with multiple myeloma (MM) (N = 5) or history of CKD (N = 3) prior to transplantation were excluded from this analysis. Patients were considered for RIC HCT if they were not eligible for transplantation using an MA regimen, either because of older age (>55 years for related donors and >45 years for unrelated donors), significant comorbidities, or extensive prior therapy. Transplant-related and outcome data were retrieved from the University of Minnesota Blood and Marrow Transplant Program Database, which prospectively collects these data on all patients transplanted at our institution. Additional data for this study were abstracted from patient medical records. Patients were treated according to clinical protocols approved by our institutional review board.

All patients are routinely followed up at our transplant program at scheduled intervals (100 days, and 6, 9, 12, 18, and 24 months) until at least 2 years after transplantation. They are seen more frequently within or after the first 2 years, as clinically indicated at the discretion of their transplant physician. All creatinine levels included in this study were measured at our hospital laboratory.

Conditioning Regimen

MA and RIC regimens used at our institution have been described previously [13-17]. Briefly, patients undergoing MA HCT received a regimen consisting of TBI and cyclophosphamide (Cy) with or without fludarabine (Flu). RIC regimens consisted of TBI with either Cy and Flu or busulfan (Bu) and cladribine (Clad). The TBI dose in MA regimens was 1320 cGy (165 cGy twice daily × 4 days) and in RIC regimens was 200 cGy (single fraction), and was given without kidney shielding. Our GVHD prophylaxis and treatment regimens have also been described previously [13,15,17,18]. All patients received GVHD prophylaxis with cyclosporine (CSA) (days −3 to at least +100), with trough levels maintained between 200 and 400 ng/mL and either methotrexate (MTX) or mycophenolate mofetil (MMF).

Study Definitions

CKD was defined according to the National Kidney Foundation guidelines as a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 for 3 months or more [19]. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation (GFR [mL/min/1.73 m^2] = 186 × [serum creatinine]$^{-1.154}$ × [age] $^{-0.203}$ × [0.742 if female] × [1.210 if African American]) [20]. CKD after HCT was defined as persistent decrease in GFR for at least 3 months anytime after 180 days posttransplant. The first occasion when a decrease in GFR was noted was considered as the time of onset of CKD. A >50% decrease in GFR compared to baseline within the first 6 months post-HCT was classified as AKI [21].

Patients with the following diagnoses were classified as having low-risk disease: acute leukemia in first complete remission, chronic myelogenous leukemia (CML) in first chronic phase, myelodysplastic syndrome (MDS), and nonmalignant hematologic diseases; high-risk disease included all other diagnoses. HCT comorbidity index (HCT-ci) scores, as described by Sorror et al. [22], were retrospectively assigned to all patients and were categorized as low (score 0), intermediate (score 1-2), or high (score ≥3).

Statistical Analysis

Comparison of patient and transplant characteristics between MA and RIC groups was performed using chi-square, Fisher's exact, or Wilcoxon's rank sum test, as appropriate [23]. The cumulative incidence of CKD was calculated by treating deaths from any cause as a competing risk [24].

Cox regression analysis was performed to evaluate potential risk factors for CKD. In addition to conditioning regimen intensity (MA versus RIC), variables considered in the multivariate model included age, ethnicity (white versus other), sex (male versus female), any smoking history pre-HCT (yes versus no), history of hypertension or diabetes pre-HCT (yes versus no), body mass index at HCT (<25 kg/m^2 versus 25-29.9 kg/m^2 versus ≥30 kg/m^2), HCT-ci score at HCT (low versus intermediate versus high), donor type (related versus unrelated), AKI within first 6 months post-HCT (none versus moderate versus severe), use of CSA for >6 months (yes versus no), grade II-IV acute GVHD (aGVHD) (yes versus no), and chronic GVHD (cGVHD) (yes versus no). Because all patients included in this study had survived for at least 1 year, aGVHD and cGVHD were considered as categoric instead of time-dependent variables. Use of CSA for >6 months, aGVHD and cGVHD were not significantly correlated; hence, all 3 variables were included in the risk-factor analysis. The multivariate models were adjusted for time since HCT and for baseline GFR.

Event times were measured from date of transplantation to date of death or last contact. All *P*-values were 2 sided. Analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Study eligibility criteria were met by 221 patients (MA = 117, RIC = 104). Patient- and transplant-related characteristics of the 2 groups are described in

Table 1. *Patient and Transplant Characteristics*

Factors	MA (N = 117)	RIC (N = 104)	*P*-value
Median age at HCT (range), years	38 (19-59)	54 (19-69)	<.01
Sex			1.00
Male	72 (62%)	64 (62%)	
Female	45 (38%)	40 (38%)	
Smoker			.34
Yes	31 (27%)	37 (36%)	
No	85 (73%)	66 (63%)	
Missing	1 (1%)	1 (1%)	
Hypertension pre-HCT			<.01
Yes	8 (7%)	23 (22%)	
No	109 (93%)	81 (78%)	
Diabetes mellitus pre-HCT			.23
Yes	5 (4%)	9 (9%)	
No	112 (96%)	95 (91%)	
BMI at HCT			.01
≤24.9 kg/m^2	52 (44%)	36 (35%)	
25-29.9 kg/m^2	50 (43%)	38 (37%)	
≥30 kg/m^2	15 (13%)	30 (29%)	
Median baseline GFR (range), mL/min/1.73m^2	112 (64-218)	96 (66-183)	<.01
HCT-ci score at HCT			.39
Low	36 (31%)	25 (24%)	
Intermediate	42 (36%)	36 (35%)	
High	39 (33%)	43 (41%)	
Diagnosis			<.01
Acute leukemia/MDS	69 (59%)	43 (41%)	
Chronic leukemia	20 (17%)	7 (7%)	
Lymphoma	17 (15%)	34 (33%)	
Other	11 (9%)	20 (19%)	
Disease status at HCT			.30
Standard risk	61 (52%)	47 (45%)	
High risk	56 (48%)	57 (55%)	
Donor type			.01
Related donor	62 (53%)	42 (40%)	
Unrelated donor	17 (15%)	8 (8%)	
Umbilical cord blood	38 (32%)	54 (52%)	
AKI within first 6 months	102 (87%)	85 (82%)	.33
CSA use >6 months	50 (43%)	36 (35%)	.22
Acute grade 2-4 GVHD	56 (48%)	61 (59%)	.11
Chronic GVHD	56 (49%)	48 (46%)	.80
Median follow-up (range), months	28 (12-75)	25 (12-67)	.01

MA indicates myeloablative; RIC, reduced-intensity conditioning; HCT, hematopoietic cell transplantation; BMI, body mass index; HCT-ci, hematopoietic cell transplantation specific comorbidity index; MDS, myelodysplastic syndrome; AKI, acute kidney injury; GFR, glomerular filtration rate; CSA, cyclosporine; GVHD, graft-versus-host disease

Table 1. MA HCT recipients were younger at HCT (median age 38 versus 54 years, $P < .01$), were less likely to be obese (13% versus 29%, $P = .01$), were less likely to have a prior history of hypertension (7% versus 22%, $P < .01$), and were more likely to receive a matched related donor graft (53% versus 42%, $P = .01$). MA HCT recipients also had a higher baseline GFR (median 112 versus 96 mL/min/1.73 m^2, $P < .01$). The 2 groups were otherwise comparable with respect to prevalence of diabetes mellitus and history of smoking prior to HCT, HCT-ci scores, disease status at HCT, duration of CSA use, and rates of posttransplant AKI, aGVHD, and cGVHD. None of the patients received an autologous HCT prior to their allogeneic HCT. MA conditioning regimens included Cy/TBI (N = 39) or Cy/Flu/TBI (N = 78). RIC regimens consisted of Cy/Flu/TBI (N = 99) or Bu/Clad/TBI (N = 5). Median follow-up duration was 28 months (range: 12-75 months) for the MA and 25 months (range: 12-67 months) for the RIC groups. For these 1-year survivors, overall survival (OS) at 2 years posttransplant was 89% for MA and 77% for RIC recipients.

Incidence of CKD

Overall, 60 patients developed CKD with a 3-year cumulative incidence rate of 29% (95% confidence intervals [CI], 22%-35%). These included 30 patients each from the 2 cohorts, resulting in a 3-year cumulative incidence rate of 28% (95% CI, 19%-36%) in the MA and 29% (95% CI, 20%-38%) in the RIC groups ($P = .44$) (Figure 1). The median time from transplant to development of CKD was 11 months (range: 6-29 months) and 9 months (range: 6-18 months), respectively. Among patients who developed CKD, 75% did so within 1 year of transplantation. Late-onset CKD, with onset >1 year after HCT, was more prevalent in the MA group (N = 11) compared to the RIC group (N = 4). Severe CKD (GFR <30 mL/min/1.73 m^2) developed in 2 patients, with 1 requiring hemodialysis. Among the remaining patients with moderate CKD (GFR 30-59 mL/min/1.73 m^2) (N = 58), only 2 had progression to end-stage renal disease (ESRD) requiring hemodialysis at a median follow up of 22 months (range: 1-53 months) from the onset of chronic renal impairment.

The most common syndrome encountered in patients developing CKD was that of nonresolving AKI with a continued decrease in GFR (N = 45). Late-onset CKD because of multiorgan failure and medications

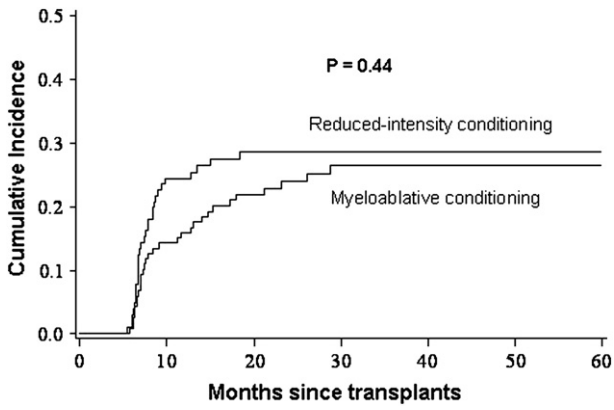

Figure 1. Cumulative incidence of CKD after allogeneic HCT.

was seen in 13 patients. Thrombotic microangiopathy was the cause of late-onset CKD in 2 patients.

We also analyzed the change in GFR within the first year posttransplant. For our cohort, who had survived for at least 1-year posttransplant, a similar decrease in GFR was noted for both MA and RIC recipients (Figure 2).

Risk Factors for CKD

In multivariate analysis, conditioning regimen intensity had no impact on the risk of developing CKD (relative risk [RR] for MA regimen, 1.50 [95% CI, 0.78-2.89] versus RIC regimen) (Table 2). Factors independently associated with an increased risk of CKD in 1-year survivors of allogeneic HCT were age at transplantation, AKI within first 6 months post-HCT, grade II-IV GVHD and CSA use for >6 months. The risk factors for developing CKD were the same as for the whole cohort on subgroup analyses limited to each conditioning regimen, except for age, which was not predictive for CKD in recipients of MA conditioning.

Table 2. *Risk Factors Predicting Chronic Kidney Disease after Allogeneic Hematopoietic Cell Transplantation*

Factor*	RR of CKD (95% CI)	*P*-value
Conditioning regimen		
RIC†	1.00	0.22
MA	1.50 (0.78-2.89)	
Age (each year increase)	1.03 (1.00-1.06)	0.05
AKI within first 6 months		
No†	1.00	0.02
Yes	4.03 (1.22-13.27)	
Acute grade II-IV GVHD		
No†	1.00	0.02
Yes	2.01 (1.12-3.61)	
CSA use >6 months		
No†	1.00	<0.01
Yes	3.49 (1.97-6.18)	

RR inicates relative risk; CKD, chronic kidney disease; CI, confidence interval; RIC, reduced-intensity conditioning; MA, myeloablative conditioning; AKI, acute kidney injury; GFR, glomerular filtration rate; GVHD, graft-versus-host disease; CSA, cyclosporine.

*Adjusted for time since transplant and baseline GFR.

†Indicates reference value.

DISCUSSION

We report a relatively high but comparable incidence of late-onset CKD in long-term survivors of MA and RIC HCT. The advantage of using less intense doses of chemotherapy and TBI in conditioning is potentially offset by the typical older age and presence of comorbidities in recipients of RIC HCT. Also, risk factors independent of conditioning regimen intensity, such as aGVHD and use of CSA, have an important role in the development of CKD. A global decline in GFR occurs early posttransplant irrespective of conditioning regimen intensity with incomplete recovery by 1 year. CKD develops relatively early after transplantation, and typically is the result of continued decrease in GFR following an early posttransplant renal insult.

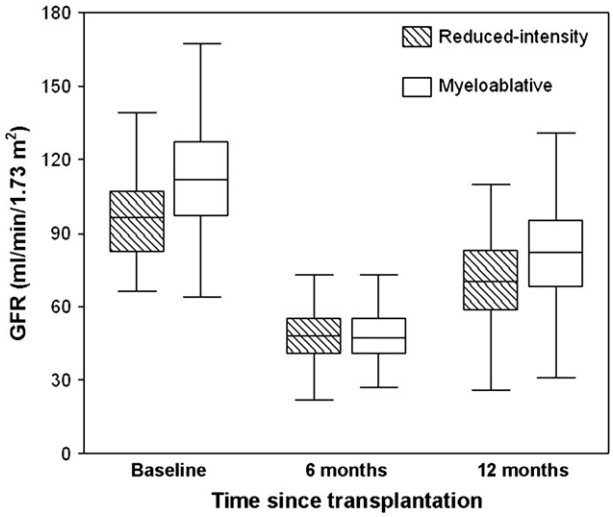

Figure 2. Change in glomerular filtration rate (GFR) among myeloablative (N = 117) and reduced-intensity (N = 104) allogeneic hematopoietic cell transplant recipients over time. All patients included in this study had survived for at least 1 year or more after transplantation. Each box-plot represents the range of GFR observed; the ends of the boxes represent the 25th and 75th percentiles, the bars indicate the 10th and 90th percentiles, and the line shows the median.

Only 1 other study has systematically investigated the incidence and risk factors of CKD after RIC HCT. Weiss et al. [2], in a retrospective cohort study of 122 nonmyeloablative HCT recipients, reported development of CKD in 66% patients at 1 year posttransplant. Although the MDRD equation was used to calculate GFR, CKD was defined as reduction in GFR by 25% or greater compared to baseline, and included patients who survived for 6 months post-HCT. This more liberal definition of CKD may have overestimated the incidence of CKD in their cohort, because 75% of a normal GFR may not lead to serious or progressive CKD. Nevertheless, their study highlights the problem of CKD in survivors of RIC HCT. They reported that acute renal injury, previous autologous HCT, long-term calcineurin inhibitor use, and extensive cGVHD were independently associated with CKD.

A significant predictor for CKD was AKI in the early posttransplant period. AKI is a well described risk factor for CKD despite the various definitions used [1,2,25,26]. Both the MA and RIC cohorts in our study had similar frequency of AKI. aGVHD was an independent risk factor for CKD in our analysis. T cell-mediated inflammation of the renal parenchyma, systemic cytokine release, and nephrotoxicity

of calcineurin inhibitors are etiologies of GVHD-related CKD. These mechanisms are involved in both aGVHD and cGVHD [2,27]. We did not find an association between cGVHD and CKD. Patients with cGVHD are also more likely to have had previous aGVHD, and tend to be exposed to CSA for a longer period of time, and these risk factors might be more important than cGVHD in the pathogenesis of HCT-associated CKD. CSA nephrotoxicity can result from direct toxicity, hemodynamic disturbances in the renal vasculature [28], or microangiopathy secondary to the procoagulant effect of GVHD-mediated tumor necrosis factor release [29]. TBI has been postulated to be an important risk factor for CKD in HCT recipients [30,31]. However, we did not observe a difference in the risk of developing CKD among recipients of high-dose (MA) and low-dose (RIC) TBI. In a large retrospective cohort study of 1635 patients, Hingorani et al. [1] also did not find TBI to be an independent predictor of CKD.

Our study has certain limitations. Smoking has been reported to be an important risk factor for CKD [32,33]. Given the retrospective nature of our study, smoking history was recorded as an affirmative variable only, because the quantity of smoking could not be obtained reliably. Although regularly monitored and adjusted for clinical management, variations of CSA serum concentration could also have an impact on the risk of CKD, and were not accounted for in our study. The follow-up of our cohort is relatively short for a study investigating late effects of transplantation. However, CKD developed within the first year in the majority of patients with a subsequent plateau in its cumulative incidence, and the onset of CKD beyond 3 years is uncommon in this and other reported series.

In conclusion, CKD is frequent in long-term adult allogeneic HCT survivors. RIC is associated with similar risks of CKD as MA conditioning. Older age, AKI, aGVHD, and prolonged CSA exposure increases the risk of CKD. Continuous attention to even a modest decline in renal function is necessary in allogeneic HCT survivors, and studies exploring prevention strategies to limit progression to ESRD are needed.

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