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Risk factors for acute kidney injury in patients undergoing allogeneic hematopoietic stem cell transplantation

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【**Abstract**】 **Background and Objective:** Allogeneic hematopoietic cell transplantation (allo-HSCT) is a potent procedure for the treatment of hematologic diseases, yet it is associated with high risks of treatment-related complications. Except for transplant-related organ toxicities, renal insufficiencies which emerge earlier significantly limit patients' long survival. To analyze risk factors for acute kidney injury (AKI), we conducted a retrospective cohort study of 96 patients undergoing HSCT. **Methods:** During the first 100 days after allo-HSCT, all patients were evaluated for renal function by measuring serum creatinine clearance and glomerular filtration rate (GFR) with a classification below: Grade 0 (< 25%, decline in creatinine clearance), Grade 1 (⩾25% decline in creatinine clearance but < 2-fold increase in serum creatinine), Grade 2 (⩾2-fold rise in serum creatinine but no need for dialysis), and Grade 3 (⩾2-fold rise in serum creatinine and need for dialysis). Cox regression model was used to calculate the hazard ratios (HRs) of demographic data, clinical variables, and risk factors for AKI. **Results:** Twenty-eight (29.2%) patients occurred Grades 1–3 renal dysfunction (Grade 1, 14 patients; Grade 2, 12 patients; Grade 3, 2 patients), and ratios of early kidney injury increased in high-risk malignancy group (HR = 2.945, 95% confidence interval (CI) = 1.293–6.421), patients treated with myeloablative conditioning regimen (HR = 2.463, 95% CI = 1.757–4.320), and patients with acute GVHD (HR = 3.553, 95% CI = 1.809–6.978), sepsis (HR = 3.215, 95% CI = 1.189–6.333), or hepatic veno-occlusive disease (VOD) (HR = 3.487, 95% CI = 1.392–6.524). Whereas, HLA histocompatibility showed no striking increased risk for acute renal injury (HR = 1.684, 95% CI = 0.648–4.378). The survival rate was lower in patients with severe nephrotoxicity (21.4%) than in patients without nephrotoxicity (70.6%) (P = 0.001). **Conclusions:** Nephrotoxicity is the primary risk factor for AKI, severely impacting on survival. Sorts of risk factors mentioned will be useful for evaluation for kidney function of patients undergoing allo-HSCT.

Key words: Renal dysfunction, risk factors, hematopoietic cell transplantation

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been shown to provide a potential curative option for a variety of hematological and non-hematological diseases[1]. However, HSCT may be associated with a high rate of treatment-related complications such as organ toxicity, graft versus host disease (GVHD), preconditioning impairment, and immunodeficiency[2]. Besides, renal insufficiency is a very common organ dysfunction after HSCT[3], and acute renal failure (ARF), defined as a double level of the pre-transplantation serum creatinine in the first 4 weeks after transplantation, as reported previously, occurs in 5%–54% of HSCT recipients[3-6]; many factors such as

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tumor lysis syndrome (TLS), marrow infusion toxicity, infections and nephrotoxicity of drugs could have contributed to ARF[4,7]. Owing to seldom relative studies on risk factors for ARF in patients treated with myeloablative conditioning regimen and with non-myeloablative conditioning regimen, we conducted a retrospective study to investigate these factors and attempted to find effective strategies for improving overall survival rate after HSCT.

Patients and Methods

Patients

Ninety-six consecutive patients with hematological malignancies, firstly receiving allogeneic HSCT in Zhongda Hospital Affiliated Southeast University between May 2003 and December 2008, were evaluated for renal function in the first 100 days after initially receiving allogeneic HSCT. This study was approved by the Institutional Review Board of Southeast University Institute of Hematology. All recipients and donors signed informed consent before participating in the study. Of the 96 patients, 54 were male and 42 were female. The median age of patients was 28 years old (range, 8–48 years), the body surface area was (1.73 ± 0.24) m^2, and the systolic blood pressure and diastolic blood pressure were (110 ± 12/14.67 ± 1.60) and (71 ± 9/9.47 ± 1.20) mm Hg/kPa, respectively. Renal function test was undertaken at 15 days before the transplantation, and 15 days, 30 days, and 60 days after the transplantation. Renal ultrasound had been performed in all patients to exclude obstructive uropathy or renal vascular abnormality. More detailed data are shown in Table 1.

Table 1 Characteristics of 96 patients undergoing hematopoietic stem cell transplantation

Characteristic	Patient No. (%)
Diagnosis	29(30.2%)
AML	
Standard risk	17
CR1	7
CR2	
High risk	5
⩾CR3	18(18.8%)
ALL	
Standard risk	12
CR1	5
CR2	
High risk	1
NR	44(45.8%)
CML	
Standard risk	28
CP	
High risk	16
AP,BC	
MDS	
High risk	5(5.2%)
RAEB	
HLA histocompatibility	
Related 6/6 identity	47
1/6 mismatch	18
2/6 mismatch	7
Unrelated 6/6 identity	18
1/6 mismatch	5
2/6 mismatch	1
ABO compatibility	
Matched	61
Minor mismatch	16
Major mismatch	19
Donor-recipient relationship	
Unrelated	24
Sibling	72

Conditioning regimen for patients

With respect to 36 patients with HLA matched sibling donor, we adopted non-myeloablative conditioning regimen using fludarabine (30 mg/m^2 daily, day 6 to day 2 before HSCT) combined with intravenous busulfan (3.2 mg/kg daily, day 4 to day 3 before HSCT). In contrast to 60 patients with HLA mismatched related or unrelated donors, myeloablative-conditioning regimen was carried out as follows: cytarabine (2 g/m^2 daily, intravenously for 2 days), cyclophosphamide (1.8 mg/m^2 daily, for 2 days), busulfan (0.8 mg/kg administered intravenously in 12 doses for more than 3 days), simustine (Me-CCNU, 250 mg/m^2), and ATG (rabbit ATG 4 mg/kg daily, intravenously for 4 consecutive days; Fresenius AG, Oberurse, Germany).

aGVHD prophylaxis

In the study, all patients received CsA, MTX, and mycophenolate mofetil (MMF) to prevent GVHD. MTX was administered at a dose of 15 mg/m^2 intravenously on day 1 after transplantation, followed by 10 mg/m^2 intravenously on days 3, 6, and 11 after transplantation, and MMF was given at a dose of 0.5 g every 12 h orally from day 1 before transplantation to day 30 after transplantation. Principally, the dosage of CsA was commenced at 3 mg/kg daily intravenously from day 1 pre-transplantation till bowel function was normal, by which the administration of CsA was switched to 5 mg/kg every day in two divided doses by the oral route. Whole CsA concentration in blood was monitored biweekly for adjusting to a level between 200 and 400 ng/L using fluorescence polarization immunoassay, and a CsA level of > 400 ng/L was defined as the toxic level.

Supportive care

All patients were hospitalized in rooms with high-efficiency air filters and received standard antibiotic prophylactic therapy with oral trimethoprim-sulfamethoxazole. For example, ganciclovir was given 5 mg/kg per day intravenously from day 9 before transplantation to day 2 after transplantation[8]. Fluconazol was also administered at a dose of 400 mg per day intravenously from day 9 to day 2 before transplantation to the patients with prophylaxis mycotic infection. When the platelet level was below 20×10^9/L or hemoglobin was down to 70 g/L during hospitalization, component transfusion of blood was given. More importantly, blood products were irradiated throughout all treatment to minimize this source of bias.

Definition of acute kidney injury

In this study, creatinine clearance was calculated by the modification of diet in renal disease (MDRD) equation: GFR [mL/(min·1.73 m^2)] = 186 × $Pcr^{-1.154}$ × $age^{-0.203}$ × (1.212 if black) × (0.742 if female)[9], consistent with that reported in previous studies on autologous and myeloablative allogeneic HSCT[10-12]. According to the serum creatinine concentration and estimated GFR, AKI was classified as follows: Grade 0, that is, normal renal function was equivalent to a decrease in estimated GFR less than 25% of the baseline value; grade 1, renal dysfunction corresponded to a less than two-fold rise in baseline serum creatinine with a decrease in estimated GFR greater than 25% of the baseline value; grade 2, renal dysfunction corresponded to greater than two-fold rise in baseline serum creatinine without the need for hemodialysis; grade 3, renal dysfunction corresponded to greater than two-fold rise in baseline serum creatinine and the need for hemodialysis. Both grades 2 and 3 renal dysfunctions were considered as severe renal dysfunction or ARF. The statistical results including incidence of different grades of AKI in 96 patients within 100 days after allo-HSCT are fully depicted in Table 2.

Table 2 Occurrence of different grades of AKI during the first 100 days after nonmyeloablative HSCT

Grade		Before transplantation (95% CI)		After transplantation (95% CI)	
	No. of patients (%)	Cr (μmol/L)	GFR (mL/(min·1.73m^2))	Cr (μmol/L)	GFR [mL/(min·1.73m^2)]
	96 (100%)	68.4 (42,106)	109.6 (68,169)	77.6 (44,270)	93.4 (36,196)
0	68 (70.8%)	67.5 (43,101)	113.6 (79,171)	66.6 (45,110)	106.6 (64,196)
1	14 (14.6%)	73 (51,107)	107 (68,139)	113 (79,151)	67 (37,84)
2	12 (12.5%)	67 (56,80)	103 (90,123)	145 (121,169)	42 (35,52)
3	2 (2.1%)	78 (69,87)	71 (51,91)	272 (247,297)	15 (12,18)

Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; HSCT, hematopoietic cell transplantation; CI, confidence interval.

Evaluation of engraftment and chimerism

Engraftment was defined as an absolute neutrophil count of > 500/μL for first 3 successive days and a platelet count of > 20 000/μL independent of transfusions. Follow-up assessment was performed by cytogenetic analysis of bone marrow aspiration in the first, second, and third month after transplantation. Besides, chimerism was identified by DNA fingerprinting of short tandem repeat, and chromosomal fluorescent in situ hybridization (FISH)[13].

Statistical analysis

Continuous variables were described as mean ± SD, with the median range in parentheses. Comparisons of variables between the various grades of renal dysfunction were facilitated by analysis of variance, in which parameters reaching a level of $P \leqslant 0.1$ were assessed as significant using multiple Cox regressions. The Kaplan-Meier survival curves were plotted for 5-year overall survival (OS). All P values were two-tailed, and a value of $P < 0.05$ was considered as statistically significant and SPSS13.5 (statistical package for social sciences) statistical software version was used for all analysis.

Results

Totally, 96 patients were successfully engrafted. However, one patient died of relapse after transplantation. The median time of absolute neutrophil count reaching 0.5 × 10^9/L was 15 days (range, 10–26 days), and as to platelet recovery, that of the platelet count reaching 20 × 10^9/L was 20 days (range, 9–60 days).

Acute GVHD

Of 96 patients, 42 (43.75%) had developed grades I–IV acute GVHD after transplantation: grade I acute GVHD, 11 (11.46%); grade II, 19 (19.79%); and grades III–IV, 12 (12.50%).

Changes in renal function after HSCT

In 96 patients, serum creatinine increased from 68.4 (42, 106) μmol/L to 77.6 (44, 270) μmol/L ($P < 0.001$) and calculated creatinine clearance decreased from 109.6 (68, 169) mL/(min·1.73 m^2) to 93.4 (36, 196) mL/(min·1.73 m^2) ($P < 0.001$). Of 96 patients, 28 (29.2%) occurred various degrees of renal dysfunction (grade 1, 14; grade 2, 12; grade 3, 2; Table 2) within 100 days after HSCT with a median time of renal dysfunction 33 days (range, 20–96 days). However, there were no significant differences in age, gender, baseline serum albumin levels, baseline creatinine concentrations or GFR between patients with and without renal dysfunction ($P > 0.05$, respectively).

Risk factors for acute kidney injury

Univariate analysis Cox regression model was created in this study cohort (Table 3), and significant factors with the value of $P < 0.1$ were analyzed repeatedly by multivariate Cox regression for demographic data and baseline characteristics, including conditioning regimen, HLA, hepatic VOD, high-risk malignancy, sepsis, and aGVHD. Univariate analysis showed that there was no striking increased risk of AKI in those patients with HLA matched and HLA mismatched, but patients in high-risk malignancy group had higher risk of AKI than did those in standard-risk group; both sepsis and VOD were also associated with high risk of AKI. In multivariable analysis including risk factors defined by events that occurred during the first 100 days after HSCT, patients with aGVHD had a higher risk of developing AKI than did those without aGVHD. Worthy of mention is that myeloablative conditioning regimen was yet associated with high risk of AKI (Table 4).

Relapse and survival

Up to December 2008, of 96 patients, 10 relapsed after transplantation with a probability of 5-year relapse of 10.4% and 57 were alive with an incidence of 5-year overall survival of 59.4%. However, 39 patients died, of which 10 died from recurrent leukemia, 1 from engraftment failure, and 28 from transplant-related complications which included GVHD ($n = 16$), infection ($n = 9$), acute renal failure ($n = 1$), and VOD ($n = 2$). The Kaplan-Meier results of OS revealed an increase of mortality relating to the grades of AKI (grade 0, 29.4%; grade 1, 57.1%; and grades 2–3, 78.6%; $P = 0.002$) in patients undergoing allo-HSCT (Figure 1).

Table 3 Univariate analysis by Cox regression on acute kidney injury in patients undergoing allo-HSCT

Variable	Patient No.	Incidence rate (%)	*P*
Age (years)			0.503
⩽ 20	36	27.8	
> 20	60	30.0	
Sex			0.369
Male	54	31.5	
Female	42	26.2	
Disease statue			0.012
High risk	27	48.1	
Standard risk	69	21.7	
HLA histocompatibility			0.050
Matched	65	23.1	
Mismatched	31	41.9	
Donor-recipient relationship			0.391
Unrelated	24	33.3	
Sibling	72	27.8	
Conditioning Regimen			0.030
Myeloablative	60	36.7	
Non-myeloablative	36	16.7	
ABO compatibility			0.443
Matched	61	27.9	
Mismatched	35	31.4	
aGVHD			0.002
No	54	22.2	
I–II	30	23.3	
III–IV	12	75.0	
Sepsis			0.002
No	64	18.8	
Yes	32	50.0	
VOD			0.017
No	87	25.3	
Yes	9	66.7	

Table 4 Risk factors for acute renal injury by multivariate analysis adjusting for demographic and baseline characteristics

Variable	Acute renal injury			
	B	HR	95% CI	*P*
Disease status	1.182	2.945	1.293–6.421	0.030
HLA	0.521	1.684	0.648–4.378	0.285
Conditioning regimen	1.147	2.463	1.757–4.320	0.034
aGVHD	1.268	3.553	1.809–6.978	0.003
Sepsis	1.249	3.215	1.189–6.333	0.023
VOD	1.199	3.487	1.392–6.524	0.008

Abbreviations: HR, hazard ratio; CI, confidence interval; HLA, human leukocyte antigen; aGVHD, acute graft-versus-host disease; VOD, hepatic veno-occlusive disease.

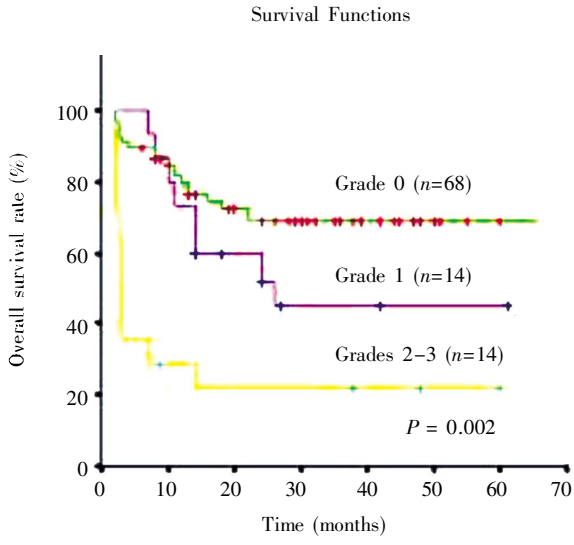

Figure 1 Kaplan-Meier curves for overall survival after allo-HSCT in 96 patients with different grades of acute kidney injury

Discussion

Following HSCT, renal insufficiency beyond GVHD is a very common problem during the first 100 days which strongly limits patients' long survival. As shown in this study, 29.2% of the patients developed grades 1–3 renal dysfunctions during the first 100 days, wherein 14.6% occurred severe renal dysfunction (grades 2–3), which can be considered as AKI. Obviously, conditioning regimen, hepatic VOD, high-risk malignancy, sepsis and aGVHD can increase the risk of AKI. Mortality is clearly associated with the severity of renal injury, and it would be higher than 78% when AKI happened. Intriguing, we found that patients with AKI were vulnerable to developing chronic kidney disease (CKD) after transplantation.

As mentioned in previous studies, the incidence of renal dysfunction ranged from 56% to 92% in cohorts of patients receiving autologous or allogeneic HSCT, with 20% requiring dialysis[14-18]. Our study showed that the incidence of renal dysfunction seems much less than that in previous studies. It is likely that conditioning regimens and patients' baseline characteristics contributed to this significance. Some studies reported that renal failure occurred in slightly more than 40% of patients within approximately a 3-month period after non-myeloablative transplantation[12,19], which is much lower than the incidence of 76% in myeloablative allogeneic transplantation (weighted mean of published studies)[3,15,19,20]. Moreover, controlling for clinical variables, the risk of developing renal failure was nearly five-fold less for non-myeloablative transplantation than for myeloablative regimens[19], and this relationship was also present for dialysis-requiring renal failure: an incidence of only 4% compared with 17% in myeloablative transplantation[3,12,15,19,20]. Clearly, conditioning regimen (HR = 2.463, 95% CI = 1.757–4.320) for patients in our study had an increased risk of AKI, consistent with that in previous studies.

In this cohort, the statistically-derived risk factors for development of renal injury in the setting of allogeneic transplantation were VOD, high-risk malignancy group, sepsis, and aGVHD. Clinically, VOD begins as a fluid-retentive state with such low urinary sodium that leads to peripheral edema and weight gain within the first few days after transplantation, mimicking the hepatorenal syndrome[21]. It should be noted that, if patients were at high risk of both bacterial and fungal sepsis pre-transplantation, renal hypoperfusion caused by vasodilation and capillary leak, coupled with cytokine-induced renal vasoconstriction, intrarenal inflammation and complement-mediated renal injury could have contributed to renal failure in the setting of sepsis. Besides, agents used to treat bacteremia and sepsis (e.g. gentamicin, amphotericin B) may be also related to nephrotoxicity in this setting. What is worthy of mention is the finding of relationship between renal injury and aGVHD with an implication that either T cell-mediated tubular injury or the inflammatory and cytokine milieu of GVHD are the proximate causes of chronic renal damage and the effect of GVHD appears to be independent of early cyclosporine use. Although much emphasis on management of these patients has been reducing the exposure to or dose of cyclosporine to prevent renal injury, we speculate that prevention of aGVHD and cGVHD or altering the cytokine and inflammatory response of GVHD will do more to reduce the incidence of renal injury following HSCT. The incidence in our study is comparable with that previous studies mentioned[12,22].

It was reported that renal dysfunction after HSCT contributed to patients' mortality[3–6,14,15]. In present study, we found that patients without renal insufficiency had a 5-year mortality of 29.4% and patients with grades 2–3 renal injury had a higher 78.6% compared with a mortality of 57.1% in those with grade 1. To conclude, renal dysfunction, coupled with sepsis is much associated with high risk of mortality in recipients after either allogeneic or autologous HSCT, which has ominous implications for survival rate of the patients[18].

Through following-up assessment, we found that development of AKI after transplantation was associated with an increased risk of CKD among long-term survivors, and the rate of CKD was relatively high in patients who had developed AKI. Compared to the incidence of CKD of 28.6% (8/28) in patients transplanted with AKI, that in those transplanted without AKI was only 8.8% (8/68) ($P < 0.05$). However, approximately 17% of patients in previous study cohort developed CKD without any laboratory evidence of

early renal injury[22]. Risk factors relating to CKD in both two groups were similar, which suggests that the mechanism of injury is the same, but perhaps becomes evident at different time points. Thus, it might be that some patients never recover from their AKI and only maintain their degrees of renal dysfunction, yet others progress to CKD.

In summary, renal insufficiency is a common organ dysfunction, which not only causes pain to patients but also obviously increases transplantation-related mortality. Since there are so many complicated etiologies and various risk factors for renal failure that efforts should be made, maybe reasonable approaches such as direct nephroprotective strategies and refinement of treatment for the extra renal targets work well. Believably, strategies to reduce AKI following transplantation could have tremendous beneficial impacts on this population, which possibly reduce severity of non-renal organ dysfunction, incidence and severity of CKD, even mortality. Owing to a small sample, further study should be required and necessarily to determine the prophylaxis and treatment of AKI after HSCT.

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