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RESEARCH ARTICLE

ACUTE RENAL FAILURE AFTER MYELOABLATIVE AND NON-MYELOABLATIVE HEMATOPOIETIC CELL TRANSPLANT: RISK FACTORS

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ABSTRACT

***Background*:** Bone marrow transplantation (BMT) is a major modality for malignant and hematologic disorders. This procedure is associated with a high morbidity and mortality such as acute kidney injury (AKI). Many factors, such as therapeutic agents, irradiation, and graft versus host disease (GVHD) can cause AKI. Bone marrow transplantation conditioning therapy in egypt is based on drugs such as busulfan and cyclo phosphamide with and without irradiation therapy. The aim of this study was to evaluate the risk factors for AKI among patients who underwent BMT.

***Methods**:* One hundred patients were rertospectively studied from time of transplant till 3 months after. Acute renal failure (ARF) was defined as a doubling of baseline serum creatinine at any time during the first 100 days post-transplant. We conducted a case-control study to identify precipitants of ARF. For each person who developed ARF, one controls were selected at random from patients who had not developed ARF as of that time. An exposure period was defined for each case as the 2 weeks prior to the day on which the matched case met the criteria for ARF. The risk of ARF in relation to demographic and anthropometric characteristics, comorbidity, types of treatment and post transplant complications was examined using univariable and multivariable conditional logistic regression models. Odds ratios for the associations with ARF were estimated, taking into account the matching.

Results: Fifty patients (50%) developed ARF at a mean 11.8 ± 6.1 days after myeloablativetrans plant versus 9.8 ± 4.1 days among non-myeloablative transplant (p=0.17). Elevated risks were observed in patients who were hypertensive (OR 4.25; 95%CI 1.45–29.95) ,patient who had post transplant ICU admission (OR 7.57;95%CI 0.79–16.55), those with sinusoidal obstruction syndrome (SOS) (OR 4.16; 95%CI 2.29–38.38), high cyclosporine trough level (OR 2.96;95%CI 0.79–16.55) , and those with post transplant weight gain (OR 2.95;95%CI 0.79–16.55). Neither graft versus host disease (GVHD), nor CMV reactivation was associated with an increased risk of ARF.

***Conclusion**:* The cumulative incidence of ARF after HCT remains high. Cyclosporine trough level and presence of hepatic sinuosoidal injury increased the risk of ARF within the first 100 days after HCT. Higher levels of serum creatinine at baseline were associated with a higher risk of ARF.

INTRODUCTION

There are three major SCT modalities that include autologous SCT (auto), myeloablative allogeneic SCT (m-allo) and non-myeloablative allogeneic SCT (nm-allo), with selection dependingon stem cell sources and preconditioning procedures[1]. Hematopoietic cell transplant (HCT) is an increasingly utilized treatment for many malignancies, aplastic anemias, and certain inborn errors of metabolism. However, patient survival may be limited by substantial treatment-related toxicities. Among the most severe of these toxicities is acute renal failure (ARF), which occurs frequently in the first 100 days following HCT. Mortality rates among transplanted patients with renal disease in this setting are higher than among those who retain normal renal function [2-5].Schrier *et al.*[1] showed the frequency of acute kidney injury (AKI) increased significantly from auto(21%) to nm-allo (40%) to m-allo (69%).In 2 large retrospective reviews of patients undergoing HCT in the 1980s, the frequency of ARF (defined asa doubling of baseline serum creatinine within the first30 days post-transplant) was 26% of 275 patients and53% of 272 patients, respectively [2,3]. Identified risk factors included sinusoidal obstruction syndrome, older age, jaundice, weight gain, and exposure to amphotericin B [2,3]. In other study, hepatic toxicity, sinusoidal obstruction syndrome, and lung toxicity were

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associated with an increased risk of ARF[5]. The conditioning regimen of cyclo phosphamide and total body irradiation has also been implicated in pediatric studies[4-6]. We studied a cohort of patients transplanted with allogeneic donor cells following a uniform conditioning regimen based on drugs, consisting of busulfan and cyclophosphamide (CY), without radiation therapy, to determine risk factors related to the development of ARF.

MATERIALS AND METHODS

Patients

Between January 2013 and January 2014 allogeneic myeloablative and non-myeloablative SCT was performed on 100 adult patients aged 17–57 years, at the BMT Research Center, Naser institute Cairo, Egypt. Patient data were collected and analysed retrospectively using a database and computerized patient records. Patients gave informed were approved by the Institutional Review Board consent and were treated according to clinical protocols approved by the local investigation review board.

Stem Cell Transplantation Procedure

Patients with hematologic, nonhematologic malignancies and thalassemia major who underwent BMT after a conditioning regimen of cyclophosphamide without total body irradiation were enrolled for evaluation of risk factors for AKI post BMT. All of the consecutive 100 patients underwent an initial evaluation prior to treatment that included history and physical examination, baseline laboratory testing, chest radiography, pulmonary function tests, and electrocardiography. Patients were accepted for transplantation only if they had adequate kidney, liver, pulmonary, and cardiac functions according to the evaluation results provided by respective specialists. All of the patients had normal kidney function based on serum creatinine (Cr) levels, before transplantation.

Conditioning Regimen

All of the patients were hospitalized and the conditioning regimen included cyclophosphamide, 30 mg/kg for m-allo and 50 mg/kg for nm-allo, and busulfan16mg/kg. None of the patients received total body irradiation. In allogeneic transplantation, bone marrow and peripheral stem cells from related donors were used as the source of hematopoietic progenitors. In some patients, cryo preserved umbilical cord blood was used as the source of hematopoietic progenitor cells, as well. Broad-spectrum antibacterial prophylaxis was used for neutropenia and empiric treatment of fever.

Graft Versus Host Disease Prophylaxis

All patients received GVHD prophylaxis with cyclosporine, which started on day – 2 at a dose of 3 mg/kg/day by continuous infusion for 3–4weeks. It was thereafter given orally for 4–6 weeks at a dose that gave comparable trough levels, followed by tapering. Dose adjustments were made to keep cyclosporine trough levels between 200 and 450 ng/ml. Serum creatinine and cyclosporine trough levels were measured at least twice a week during the first month, and at least once a week thereafter until the cyclosporine was stopped. When no active GVHD was present, cyclosporine was discontinued within 3 months after transplantation. GVHD was diagnosed according to the Seattle criteria.[7]

Anti-Thymocyte Globulin Therapy

The graft was partially T-cell-depleted, as described. In recipients of his to compatibility leukocyte antigen (HLA)-matched unrelated donor or a single HLA-antigen mismatched family donor, anti-thymocyteglobulin (Rabbit ATG, Thymoglobulin, Sang stat, Amstelveen, the Netherlands) was given before cyclo phosphamide was infused.

Infection Prophylaxis

consisted of ciprofloxacin, fluconazole given orally until granulocyte counts exceeded 500 cell/ml. Cephalotin was given intravenously from day þ3 until day þ13. Co-trimoxazole480mg twice daily and valacyclovir 500mg twice daily were given orally from day þ1 until 12 months after transplantation (or longer in cases of active GVHD).

Study Design

We used a case-control study design to explore risk factors for ARF, defined as a doubling of baseline serum creatinine within the first 100 days after transplant. Baseline serum creatinine was the value obtained prior to the start of conditioning therapy. Fifty controls were selected at random from among patients in the study cohort who were event-free for at least as long as the time preceding the onset of ARF in the matched case.

An exposure period of 2 weeks prior to the onset of ARF was defined, in which potential time-varying risk factors were examined. The exposure period for a control patient was defined as the 2 weeks prior to the study day on which the matched case developed ARF. Thus, 50 cases and 50 control observation periods comprised the study population.

Patient Monitoring

The following clinical data were collected during the14 day exposure periods: daily weight, first morning pulse and blood pressure, maximum daily temperature, daily medications, total serum bilirubin, the presence of bacteremia or fungemia, and cyclosporine blood levels.

In addition to time-dependent factors, we examined the following pretrans plant patient characteristics for their association with ARF: age, gender, baseline serum Cr, weight, and serum albumin, as well as transplant related factors the occurrence of acute graft versus host disease (GVHD) and sinusoidal obstruction syndrome (SOS) developing any time

prior to the onset of ARF in the index case were also examined as potentialrisk factors.

Statistical Methods

The distributions of the continuous covariates in the cases and controls were compared using Wilcox on rank sum tests. The odds ratios (OR) were calculated using conditional logistic regression models, which take in to account the matching. All potential predictors were first evaluated in univariable conditional logistic regression models. Those parameters reaching a univariable significance level of $P \leq 0.1$ were assessed for significance in multiple conditional logistic models. The *P* values corresponding to the multiple regression model are based on the Wald test. The SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA) was used for all analyses.

RESULTS

The baseline characteristics of the 50 m-allopatients (25 cases and 25 control), 50 nm-allo patients (25 cases and 25 control) were summarized in Table 1. All patients received allografts, the majority (42%) for AML. Of 100 patients, 50 (50%) developed ARF before day +100, at median day +10 (range day+3 to +27) after transplant. Table 1 lists the mean and SD for the risk factors analyzed among cases and controls, and also shows the univariable associations between ARF and all the potential risk factors.

Table 1 Demographics and baseline characteristics of the patients before and after SCT

Variables	M-allo		Nm-allo	
	Cases N=25	Control N=25	Cases N=25	Control N=25
Age(years)	20.5±12.6	16.3±12.0	23.4±14.6	17.4±14.2
Gender(M/F)	18/7	15/10	17/8	14/11
Weight(kg)	55.6±29.5	42.8±24.9	53.6±21.9	44.2±29.2
Diagnosis				
AML	12(48%)	9(36%)		
ALL	2 (8%)			1(4%)
CML	4 (16%)	3(12%)		
BTM	4 (16%)	6(24%)		
FA			6(24%)	3(12%)
MDS		3(12%)	3(24%)	5(20%)
SOS			16(64%)	13(52%)
Others	3(12%)	4(16%)		2(8%)
History				
HTN(Yes/No)	4/21	4/21	3/22	1/24
DM(Yes/No)	2/23	1/24	2/23	0/25
RD(Yes/No)	1/24	0/25	0/25	0/25
Cr pre- SCT(mg/dl)	0.6±0.2	0.56±0.17	0.69±0.96	0.6±0.16
e GFR (ml/min)	128.9±17.9	134.7±19.1	126.3±15.8	135.1±18.2
C0 after SCT (ng/ml)	116.8±56.5	97.8±58.8	129.6±43.2	122.3±59.2
Cr level at AKI(mg/dl)	1.63±0.59	0.81±0.27*	1.95±0.39	0.81±0.24*
C0 at AKI (ng/ml)	158.4±93.5	147.5±87.2	202.8±70.6	127.8±56.3*
Cr level at 100 day(mg/dl)	0.73±0.29	0.53±0.21*	0.73±0.13	0.58±0.17*

Abbreviations: M-allo=myeloablative allogeneic transplantation; Nmallo =non-myeloablativeallogeneic transplantation; Cr=serum creatinine before transplant; AML=acute myeloid leukemia; CML=chronic myelocytic leukemia; MDS=myelodysplastic syndrome; BTM=Beta thalassemia major;FA= fanconianemia; SOS= sinusoidal obstruction syndrome; HTN=hypertension ;DM= diabetes mellitus; RD; renal dysfunction ;SCT= stem celltransplant;e GFR= estimated glomerular filtration by MDRD equation; C0=cyclosporine trough level; AKI=acute kidney injury;
Asterisk (*) indicates a significant difference between them-allo and nm-allo groups.

Table 2 Post Stem cell transplant complications

Variables	M-allo		Nm-allo	
	Cases N=25	Control N=25	Cases N=25	Control N=25
AGVHD(Yes/No)	1/24	0/25	2/23	1/24
SOS(Yes/No)	14/11	7/18*	13/12	4/21*
ICU admission(Yes/No)	0/25	0/25	6/19	2/23
CMV reactivation(Yes/No)	0/25	0/25	2/23	0/25

Abbreviations: AGVHD=acute graft versus host disease;SOS= sinusoidal obstruction syndrome; ICU=intensive care unit; CMV= cytomegalovirus Asterisk (*) indicates a significant difference between the m-allo and nm-allo groups.

Table 3 Odds ratio of acute kidney injury post stem cell transplatation with 95% confidence intervals

variable	case	control	Chi-square	P-value	Odds ratio	P-value
History of HTN						
Yes	14	5	7.294	0.0069	4.235	0.0130
no	36	45				
History of DM						
Yes	4	1	1.895	0.687	4.246	0.2023
no	46	49				
History of RD						
Yes	1	0	1.010	0.3149		
no	49	50				
ICU admission						
Yes	10	2	8.366	0.004	7.579	0.0107
no	40	48				
Acute GVHD						
Yes	3	1	1.042	0.307	3.128	0.3308
no	47	49				
S O S						
Yes	27	11	10.866	0.0010	4.162	0.0013
no	23	39				
CMV reactivation						
Yes	2	0	2.041	0.1531		
no	48	50				
C0 increase						
Yes	31	18	6.763	0.0093	2.961	0.0102
no	19	32				
Wt gain						
Yes	18	8	5.198	0.0226	2.953	0.0257
no	32	42				
Fever development						
Yes	8	6	0.332	0.5644	1.397	0.5655
no	42	44				
HTN development						
Yes	5	3	0.543	0.4610	1.278	0.4655
no	45	47				

Abbreviations: HTN=hypertension; DM= diabetes mellitus; RD; renal dysfunction AGVHD=acute graft versus host disease;SOS= sinusoidal obstruction syndrome; ICU=intensive care unit; CMV= cytomegalovirus;C0 = increase in cyclosporine trough level during exposure period

There was significant higher cyclosporine trough level at the time of AKI between Nm-allo cases and control. Table 2 showed that SOS was the most common post SCT complication among patients with AKI. Table 3 Regression analysis showed that the largest ORs for development of AKI were observed in patients who had ICU admission post SCT(OR 7.57, 95% CI 1.86–14.43), history of HTN (OR 4.23,95% CI 1.86–14.43), those who had a clinical diagnosis of SOS prior to the date of onset of ARF (OR 4.16,95% CI 1.86–14.43). The risk of ARF was also associated with a5% greater gain in weight from baseline (initial weight atclinic visit prior to the start of cyclophosphamide) to the end of the exposure period (OR 2.95, 95% CI 1.05–1.78). Also higher cyclosporine trough levels (OR 2.96, 95% CI 1.05–1.78) increase the risk of AKI in these patients.

DISCUSSION

Acute renal failure, defined as a doubling of baseline serum creatinine, remains common after SCT. In spite of recent advances in the care of patients undergoing SCT, the cumulative incidence of ARF was 50% in this cohort. Major factors associated with an increased risk of the development of ARF were identified by multivariable analysis: pre-transplant hypertension, SOS, ICU admission, increase cyclosporine trough level, weight gain post transplant. There was no evidence in the data that the incidence of ARF was related to cyclophosphamide exposure levels, sepsis, GVHD, nor older age. Unlike previous studies of ARF after HCT, all of our patients received the same conditioning regimen, allowing us to cleanly evaluate other risk factors. We investigated blood levels of cyclosporine in relation to the occurrence of ARF. Much of the renal toxicity of cyclosporine is thought to be dose dependent [8], we found that higher levels of cyclosporine were associated with an increased risk of ARF in this patient population. Our data suggest that an elevated baseline serum creatinine was associated with a high risk for ARF. Zager *et al* [3] founda high baseline serum creatinine (>0.7 mg/dL) was independently associated with the development of dialysis requiring ARF. Similarly, in the pediatric population, high pretrans plant serum creatinine has been associated with an increased risk of renal failure in the first 3 months after transplant [9].Previous studies in adults have identified SOS or elevated serum bilirubin levels (used as a surrogate marker for liver injury) as risk factors for the development of ARF[2,3,5]. In our study, the presence of SOS was associated with an increase in the risk of ARF. There isa well-known association between sinusoidal liver injury and renal insufficiency in patients after hematopoietic celltrans plant [10]. It has been postulated that portal hypertension resulting from hepatic sinusoidal injury leads to both decreased renal perfusion [11] and tubular injury [12], the former probably being the more important in the genesis of ARF. Weight gain was highly correlated with SOS. Weight gain can be a result of portal hypertension, leading to decreased renal perfusion and sodium avidity that precedes the development of ARF. Thus, weight gain likely serves as a marker of impending renal injury rather than being the result of renal injury. Zager *et al* identified weight gain within the first 21 days post-transplant as a risk factor for the development of ARF and ARF requiring dialysis. Weight gain of ≥10% of baseline at the onset of dialysis for ARF in pediatric stem cell transplant patients was associated with persistence of renal failure [4]. Though some have advocated keeping weight gain per se to a minimum (<10% fluid overload) to improve outcomes in this patient population [13], it is unclear if the weight gain is causal or the result of other insults to these patients. Thus, prevention of SOS may be the more important strategy. The reported prevalence of thrombotic microangiopathic (TMA) syndromes [hemolytic uremic syndrome (HUS) and thrombocytopenic purpura (TTP)] ranges from 2% to 21% after HCT [14-16]. The clinical spectrum of renal dysfunction in HCT patients with TMA varies from an indolent course resulting in chronic renal insufficiency to fulminant disease with acute renal failure and death. Several risk factors for TMA have been proposed: unrelated donor stem cell source [16], conditioning with TBI [17-19], age and female gender [14]; and cyclosporine exposure 15, 20–24. Our study didn't recorded any case of TTP, the presence of TMA is not a risk factor for the development of ARF in our patient population.

CONCLUSION

This study found that ARF remains a common problem after SCT, affecting 50 % of patients. In a multivariable analysis, strong risk factors were identified: history of HTN, ICU admission, SOS, weight gain, high cyclosporine trough level. Prevention, early recognition, and treatment of SOS, offer the best chance to preserve renal function in patients after SCT.

Conflict of Interest

The authors declare no conflict of interest.

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