Frequency, Risk Factors, and Outcome of Acute Kidney Injury Following Bone Marrow Transplantation at Dr Shariati Hospital in Tehran

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Introduction. 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 Iran is based on drugs such as busulfan and cyclophosphamide and without irradiation therapy. The aim of this study was to evaluate the frequency, risk factors, and mortality of AKI among patients who underwent BMT.

Materials and Methods. Acute kidney injury was defined as doubling serum creatinine from baseline at any time during the first 180 days posttransplant. The risk of AKI in relation to non-total-body-irradiation-based conditioning regimen, type of graft (allograft and autograft), comorbidities, GVHD, drug toxicity, and veno-occlusive disease were examined in 375 patients with BMT.

Results. One hundred and forty-two patients (37.6%) developed AKI at a median of 18 days after transplant. A higher frequency of AKI was observed in patients who received cyclosporine A (40%), patients with allograft BMT (42.1%), and those who developed gastrointestinal GVHD (47.3%) .The remainder AKI cases were associated with amphotericin B, veno-occlusive disease, and hemolytic-uremic syndrome.

Conclusions. The frequency of AKI in our patients with BMT remained high. Cyclosporine A and amphotericin B and the presence of GVHD and veno-occlusive disease increased the risk of AKI within the first 180 days after BMT.

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INTRODUCTION

Bone marrow transplantation (BMT), also called *hematopoietic cell transplantation*, has gained worldwide acceptance as treatment of various diseases. Currently, 15 000 patients worldwide receive BMT every year.[1] Hematopoietic cell transplantation involves administration of a high dose of chemoradiotherapy to destroy the tumor cells, and at the same time, suppress the host's immune system to prevent graft rejection.[2] In addition, posttransplant immunosuppressive drugs such as cyclosporine A and methotrexate are utilized to prevent graft versus host disease (GVHD). Organ toxicities beyond the bone marrow are common and potentially life threatening. Acute kidney injury (AKI), occurring within 180 days post-BMT, is mainly related to sepsis, nephrotoxic antibiotics, other therapeutic agents, and hepatorenal syndrome. The rate of renal insufficiency is estimated to be 26% after 180 days post-BMT.[1-3]

In the allograft, GVHD could be the main problem. The main organs involved are usually the skin, gastrointestinal tract, and liver; kidney dysfunction after BMT has been reported and there are some recent reports of GVHD-related glomerulonephritis. Acute kidney injury is an important complication. Bone marrow transplantation conditioning therapy in our center is based on drugs, consisting of busulfan and cyclophosphamide, without radiation therapy, and the in present study, we evaluated acute kidney dysfunction in patients undergoing allogeneic and autologous BMT.

MATERIALS AND METHODS

Patients

Between October 2000 and January 2002, a prospective study was done on 378 patients at the BMT Research Center, Shariati Hospital, in Tehran, Iran. Patients with hematologic and nonhematologic malignancies and thalassemia major who underwent BMT after a conditioning regimen of cyclophosphamide without total body irradiation were enrolled for evaluation of frequency and outcome of AKI and its complications. All of the consecutive 378 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 levels, before transplantation.

Conditioning Regimen

All of the patients were hospitalized and the conditioning regimen included cyclophosphamide, 140 mg/m^2, and busulfan 4, mg/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, cryopreserved 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. Antibiotics included amikacin (2.5 mg/kg initial dose, then 1.5 mg/kg every 8 hours), a third-generation cephalosporin, and vancomycin (1 g every 12 hours). If the fever persisted for more than 48 hours, then amphotericin B, 0.6 mg/kg, was added.

Graft Versus Host Disease Prophylaxis

Patients with allograft BMT received GVHD prophylaxis by cyclosporine A, 4 mg/kg, and methotrexate (6 mg/m^2 to 10mg/m^2) or cyclosporine A and prednisone, 2mg/kg. Through levels of cyclosporine A were checked for monitoring of cyclosporine A toxicities.

Patient Monitoring

The patients were monitored during their entire hospital course for complications, including sepsis (documented by positive blood cultures), hypotension (defined as systolic blood pressure < 90 mm Hg), tumor lysis syndrome, and organ toxicities (liver and gastrointestinal GVHD). The diagnosis of acute tubular necrosis was made using measurements of fraction excretion of sodium. Kidney function was assessed by the serum creatinine concentration. These parameters were measured on the day before BMT (day -1) and on days 7, 14, 21, 28, 60, 90, 100,160, and 180. Acute kidney injury was defined as doubling of serum creatinine level from baseline (day -1) at any time during the first 180 days posttransplant. Acute kidney injury was classified according to the period after BMT: immediate, first 5 days (tumor lysis syndrome and tumor lysis syndrome-marrow toxicities); early, after 5 days (veno-occlusive disease, radiation, drugs, and GVHD); and late, after 1 month (hemolytic-uremic syndrome and glomerulonephritis). Veno-occlusive disease of the liver was defined as the occurrence of at least 2 of the following criteria within 20 days of transplantation: (1) hyperbilirubinemia (total serum bilirubin concentration greater than 2 mg/dL), (2) hepatomegaly or right upper quadrant pain, and (3) sudden unexplained weight gain (more than 2% of baseline body weight).

Statistical Analyses

Quantitative variables were reported as mean ± standard deviation. For dichotomous variables, the frequency of positive occurrences was given along with their corresponding percentages. Comparisons of continuous variables between various groups of kidney dysfunction were facilitated using the Student *t* test. Probabilities

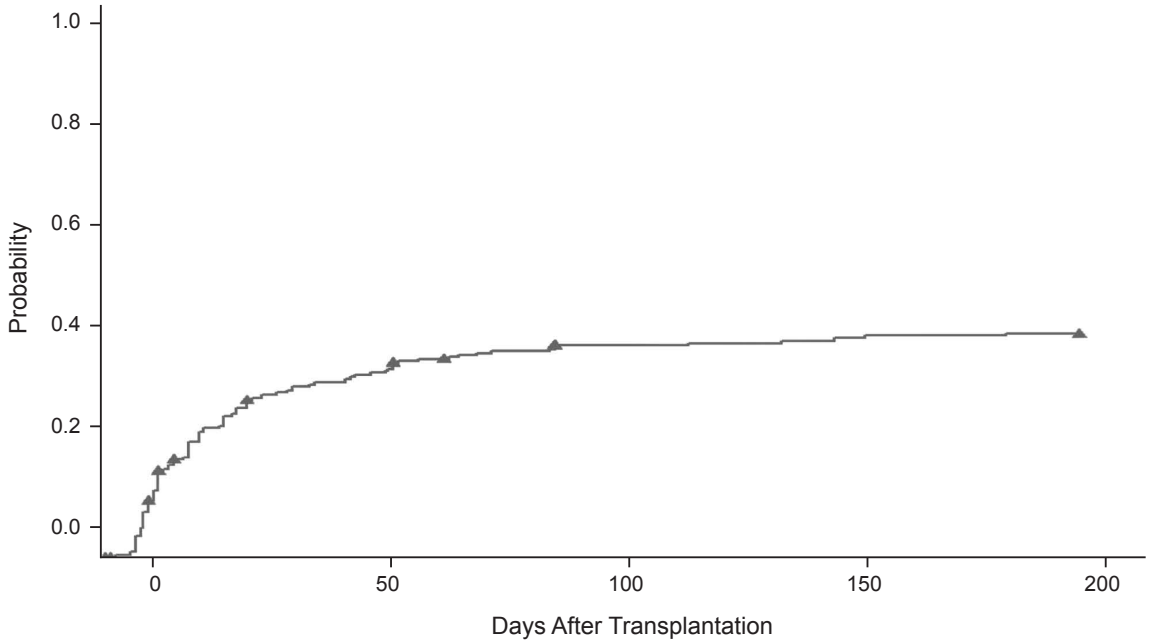
of AKI incidence were estimated by the Kaplan Meier method and compared between categories of potential risk factors by the log-rank test in the univariate analysis. The SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA) was used for all analyses.

RESULTS

A total 378 patients with a mean age of 18 ± 13 years (range, 3 to 59 years) were studied. They were 154 women and 224 men. Allograft BMT was performed for 292 patients, and autograft BMT, for 86. Cyclosporine A was administered in 292 patients (77.2%). The frequency of AKI was 37.6% (142 patients). Of all AKI episodes, 80% occurred within 1 month following BMT (Table 1).

Table 1. Acute Kidney Injuries After Bone Marrow Transplantation Classified Based on Time of Onset

Acute Kidney Injuries	Patient (%)
Immediate	
Marrow toxicity	2 (1.4)
Early	
Veno-occlusive disease	3 (2.1)
Drug toxicity	88 (61.9)
Gastrointestinal GVHD	79 (55.6)
Late	
Hemolytis uremic syndrome	7 (4.9)
Glomerulonephritis	3 (2.1)



Probability of acute kidney injury after bone marrow transplantation.

Table 2. Frequency of Acute Kidney Injury After Bone Marrow Transplantation Based on Pathologic Classification*

Acute Kidney Injuries	Autograft	Allograft	All
Prerenal	1 (5.3)	15 (12.3)	16 (11.3)
Veno-occlusive disease	0	3 (3.2)	3 (2.1)
Systemic capillary leak syndrome	0	2 (1.6)	2 (1.4)
Hypovolemia	1 (5.3)	10 (8.1)	11 (7.7)
Renal	18 (94.7)	108 (87.8)	126 (88.7)
Acute tubular necrosis	17 (89.5)	102 (82.9)	119 (83.8)
Nephrotoxic (drugs)	0	86 (69.9)	86 (60.5)
Ischemic	15 (78.9)	16 (13.0)	31 (21.8)
Marrow infusion toxicity	2 (10.5)	0	2 (1.4)
Hemolytic-uremic syndrome	0	6 (4.9)	6 (4.2)
Glomerulonephritis	1 (5.3)		1 (7.0)
Postrenal	0	0	0
Total	19	123	142

*Values in parentheses are percentages as proportions to the total values.

The median time to AKI after transplantation was 18 days (range, 1 to 185 days). The Figure shows the probability of AKI incidence during the days after transplantation. Of 292 patients who received allograft BMT, 123 (42.1%) had AKI and of 86 patients who received autograft BMT, 19 (22.1%) had AKI ($P < .001$). The frequency of acute kidney injury according to classification for prerenal, renal, and postrenal is shown in Table 2. Acute tubular necrosis was the most frequent underlying cause (126 patients; 88.7%), of which nephrotoxic acute tubular necrosis was dominant (88 patients; 69.8%). Table 3 shows the drugs related to the acute tubular necrosis events. Of 167 patients with gastrointestinal GVHD, 79 had acute kidney failure (47.3%; $P < .001$). Table 4 shows causes of AKI in patients with gastrointestinal GVHD.

In the univariate analysis, risk factors related to the development of AKI were age older than 16 years ($P < .001$), allogeneic transplantation ($P = .003$), cyclosporine administration for GVHD prophylaxis ($P < .001$), and using nephrotoxic medications (serum cyclosporine level higher than 209 µg/L; $P < .001$). In multivariate analysis, AKI did not have a significant association with sex, underlying disease, drugs, or blood pressure. The only factors remained significant in multivariate analysis were age (relative risk, 2.058; 95% confidence interval, 1.385 to 3.058), cyclosporine toxicity (relative risk, 5.988; 95% confidence interval, 3.952 to 9.091); however, because a strong association of cyclosporine toxicity with other factors such as graft type could mask effects of other risk factors, the analysis was performed again after removing the cyclosporine toxicity variable. In the second analysis, allograft patient's age older than 16 years remained as an independent predictor of AKI (Table 5). Risk factors related to the development of AKI were age older than 16 years ($P < .001$), allograft BMT ($P < .001$), and cyclosporine for GVHD prophylaxis ($P < .001$). There were no significant correlations between the underlying disease, sepsis, conditioning therapy, and gender with AKI. None of the patients required hemodialysis, and the overall mortality was zero (Table 6). Sixteen patients died during the first 200 days after transplantation. Although 6 of them experienced AKI, none died due to renal insufficiency and their serum creatinine level had returned to the normal level before death.

Table 3. Drugs Related to Acute Kidney Injury

Drug	Percent
Cyclosporine	40.0
Amikacin	14.2
Amphotericin	10.3
Amikacin and amphotericin	8.3
Amikacin, amphotericin, and cyclosporine	27.2
Methotrexate	0

Table 4. Acute Kidney Injury in Gastrointestinal Graft Versus Host Disease

Acute Kidney Injuries	Percent
Prerenal	2.6
Veno-occlusive disease	30.0
Systemic capillary leak syndrome	18.0
Hypovolemia	52.0
Renal	97.4
Cyclosporine toxicity	62.0
Others	28.0
Ischemic	0
Hemolytic-uremic syndrome	8.9
Postrenal	0

Table 6. Comparison of Bone Marrow Transplant Patients With and Without Acute Kidney Injury

Parameter	AKI, %	No AKI, %	*P*
BMT type			
Allograft	42.1	57.9	
Autograft	22.1	77.9	< .001
Age > 16 years	54.2	45.8	< .001
Sepsis	27.2	72.5	.06
Graft versus host disease	47.3	52.7	< .001
Veno-occlusive disease	33.3	66.7	.54
Hemolytic-uremic disease	100	0	< .001

Table 5. Risk Factors of Acute Kidney Injury in Multivariate Analysis

Factor	Relative Risk (95% Confidence Interval	*P*
For all patients		
Cyclosporine toxicity	5.988 (3.952 to 9.091)	< .001
Age	2.058 (1.385 to 3.058)	< .001
For allogeneic transplant patients		
Cyclosporine toxicity	6.173 (4.032 to 9.434)	< .001
Age	1.938 (1.300 to 2.882)	.001

DISCUSSION

Bone marrow transplantation is becoming an increasingly utilized procedure to treat a variety of hematological malignancies. The major indications include hematological malignancies such as acute myeloid leukemia, acute lymphoid leukemia, and chronic myeloid leukemia, as well as marrow failure states such as aplastic anemia and genetic disorders (beta-thalassemia). In addition to other transplant-related organ toxicities, and in spite of recent advances in the care of patients undergoing BMT, the occurrence of acute kidney injury, defined as doubling serum creatinine from the baseline, is a common complication following transplantation.[4,5,6,7] In this study also, 37.6% of the patients developed AKI. To our knowledge, this is the first study in Iran to evaluate acute kidney injury post-BMT in patients who received non-total-body-irradiation-based conditioning regimen.

The major factor associated with an increased risk of the development of AKI in the present study was cyclosporine toxicity (40%). Cyclosporine has been used for almost 20 years in the prevention and treatment of GVHD. While cyclosporine has many advantages, including no myelosuppression, its major drawback is renal toxicity.[8] The addition of amphotericin B, frequently needed for treatment of fever and neutropenia, in combination with cyclosporine further increases renal toxicity.[5,8] In the present study, amphotericin B and cyclosporine could offer combined nephrotoxicity. All of our patients received the same conditioning regimen. Also, we investigated blood levels of cyclosporine in relation to the occurrence of AKI. Much of the renal toxicity of cyclosporine is thought to be dose dependent. Adjustments in dose should be made to maintain lower levels and when kidney dysfunction is present. However, Zager and colleagues found a high baseline serum creatinine (> 0.7 mg/dL) was independently associated with the development of dialysis-requiring acute kidney failure.[9,10] Differences in the findings of our study and their conclusion may also stem from the fact that all of our patients underwent uniform non-total-body-irradiation-based conditioning regimen.

Liver disease is also commonly viewed as a side effect of BMT, and a particular concern is the development of hepatic veno-occlusive disease.[10,11] Previous studies in adults have identified elevated serum bilirubin levels (used as a surrogate marker for liver injury) is a risk factor of the development of acute kidney failure.[12] In this study, the presence of veno-occlusive disease in 3 patients was not associated with an increase in the risk of acute kidney failure (P = .54). However in other studies, a well-known association between sinusoidal liver injury and renal insufficiency has been reported in patients after hematopoietic cell transplantation.[13,14] Risk factors of the development of hepatic veno-occlusive disease include increasing age, pre-existing hepatic disease, fever, cytomegalovirus seropositivity, and medications (estrogen, progestin, amphotericin, methotrexate, and agents frequently used as part of conditioning regimens such as busulfan and cyclophosphamide). Overall, hepatic veno-occlusive disease occurs more commonly in allogeneic compared to autologous transplantation.[12,15] The reduced incidence in autologous transplantation may be due to the absence of methotrexate, since there is no risk of GVHD, and because of more rapid engraftment. In this study, hepatic veno-occlusive disease was not common (n = 3), probably because of the much lower intensity of the conditioning.

The reported prevalence of thrombotic micro-angiopathic syndromes (hemolytic-uremic syndrome and thrombocytopenic purpura) ranges from 2% to 21% after hematopoietic cell transplantation.[16-18] The clinical spectrum of kidney dysfunction in BMT patients with hemolytic-uremic syndrome varies from an indolent course resulting in chronic renal insufficiency to fulminant disease with acute kidney failure and death. Several risk factors of hemolytic-uremic syndrome have been proposed: unrelated donor stem cell source, conditioning with total body irradiation, age and gender, and cyclosporine exposure.[16,18-24] We evaluated the presence of hemolytic-uremic syndrome or isolated it as a risk factor of the development of AKI in our patients, which occurred in 1.9% (P < .001).

The finding of AKI among patients receiving amphotericin B is not surprising, because the nephrotoxicity of conventional amphotericin is well known,[25] as is its association with kidney failure in the BMT population. In this study, 10% of AKIs were associated with amphotericin B. Portanova and colleagues found that those receiving liposomal amphotericin were less likely to develop nephrotoxicity compared to those who received conventional amphotericin (32% versus

66%, respectively), and fewer patients in the liposomal group required dialysis.[26] In this study, the number of patients receiving amphotericin was not small, and preferential administration of liposomal formulation to patients otherwise at high risk of AKI could have helped them to decrease the occurrence of acute kidney failure. Amphotericin B is also thought to impose an early acute decrease in renal blood flow.[6,27,28] Fortunately, newer antifungal drugs such as fluconazole, itraconzole, voriconazole, and caspofungin are now available for some indications formerly covered by amphotericin. Depending on the end points chosen, each of these medications has been shown to be equally efficacious as amphotericin is, but with better safety profiles.[29]

The incidence of AKI in patients undergoing autologous transplantation is much lower (22%) than in allogeneic transplantation.[2,30] The present results demonstrated that allogeneic transplantations carry a much higher AKI rate (42.1%, $P < .001$). Of the 296 allogeneic transplant patients in this study, 123 (42.1%) had AKI, mainly during the first month of treatment. The reasons for this vast difference are two-fold. First, in autologous transplantation, there is no GVHD. Graft versus host disease may contribute to nephrotoxicity directly and indirectly (prophylaxis via calcineurin inhibitors). Second, because there are no foreign cells, more rapid engraftment occurs (resulting in less cytopenia, sepsis, and nephrotoxic antimicrobials).

CONCLUSIONS

Kidney dysfunction occurs within 180 days after allogeneic BMT in the majority of the cases. The frequency of kidney dysfunction was dramatically greater in allogeneic than autologous transplantation (42.1% versus 22.1%) in our BMT center in Tehran, Iran. The age, BMT type, gastrointestinal GVHD, and cyclosporine toxicity were significantly correlated with developing kidney dysfunction. Using non-total-body-irradiation-based conditioning regimen clearly has a good impact on the clinical management of the allogeneic transplant recipient. The BMT in older patients and allograft donor transplants need more GVHD prophylaxis regimen, and they are also associated with higher rate of fungal infections, which are usually treated with nephrotoxic drugs. The time course of kidney failure here suggests that any potential therapeutic agent to prevent kidney dysfunction needs to be started soon after the transplantation and continued for 2 to 3 weeks in order to prevent kidney dysfunction.

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CONFLICT OF INTEREST

None declared.

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