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CLINICAL STUDY

Acute renal failure after myeloablative allogeneic hematopoietic stem cell transplantation: incidence, risk factors, and relationship with the quantity of transplanted cells

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ABSTRACT

Aim: Acute renal failure (ARF) after hematopoietic stem cell transplantation (HSCT) is a widespread complication leading to considerable morbidity and mortality. The present study aims to determine the incidence and risk factors of ARF and to investigate whether there exists a relationship between the renal injury indicators and quantity of the transplanted stem cells in a uniform patient population after allogeneic myeloablative HSCT. **Methods:** Patients undergoing myeloablative allogeneic HSCT from 2007 to 2008 were monitored prospectively in terms of their renal functions during the first 100 days after transplantation. ARF was defined as a twofold rise in serum creatinine concentration of baseline value or a >50% decrease in creatinine clearance and classified into three grades. **Results:** ARF occurred in 51.3% of patients over a period of 100 days after HSCT. ARF developed in 12 (60.0%) patients within the first 2 weeks, whereas in 8 (40.0%) of them ARF development was observed within 2–4 weeks. No correlation was found between ARF development and the quantity of the infused hematopoietic stem cells. Additionally, we were not able to identify a particular cause which was significantly associated with the occurrence of ARF after HSCT. **Conclusion:** A 51.3% incidence of ARF was found in patients after myeloablative allogeneic HSCT. ARF in HSCT patients could not be linked to a single cause. Rather a combination of multiple risk factors seems to be responsible for ARF development.

Keywords: myeloablative allogeneic; acute renal failure; hematopoietic stem cell transplantation; chemotherapy; graft-versus-host disease

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has increasingly been used as a successful therapeutic modality to cure patients with malignant hematologic disorders and also some advanced non-hematologic malignancies. However, a number of complications still limit patient survival evidently. Among those, acute renal failure (ARF) is realized to be a remarkably widespread complication leading to considerable morbidity and mortality.^{1–4} There are several factors which can contribute to acute renal injury in this special group of patients including tumor lysis syndrome (TLS), sepsis, antibiotic nephrotoxicity, hepatic veno-occlusive disease, thrombotic microangiopathy, graft-versus-host disease (GVHD), and nephrotoxicity because of antimicrobial agents and calcineurin inhibitors.

From another point of view, stem cells in general are believed to have high tissue-regenerating capacity and their restorative potential for renal repair has been shown by a number of recent studies.^{5–8} Renoprotective activity of already known stem cell lineages is recognized not only in ischemically injured kidneys^{5,7,8} but also in cisplatin-induced toxicity.⁹ Considering this highly regenerating and self-renewing ability of stem cells, the dilemma of high ARF rates seems somewhat surprising.

The high incidence of ARF after HSCT was mostly linked to treatment-related toxicity. Additionally, some known risk factors for renal injury were reestablished and specific situations like GVHD were emphasized to have a role in the pathogenesis of acute renal injury. An important paucity in previous investigations was that the majority of them were conducted on

heterogeneous patient groups with the exception of a few researches which really had paid attention to form uniform patient populations.

The goal of the present study was to determine the incidence and risk factors of ARF and to investigate whether there exists a relationship between the renal injury indicators and the quantity of transplanted hematopoietic stem cells in a uniform patient population after allogeneic myeloablative HSCT.

METHODS

Patient selection and initial evaluation

This is a single-center prospective clinical study which started in March 2007 at the Bone Marrow Transplantation Unit of Erciyes University in Kayseri, after the approval of the local ethics committee. The time period for recruiting patients was ended in March 2008. To determine the baseline clinical and laboratory data, all eligible patients who signed the informed consent form were closely monitored prospectively in terms of their renal functions during the first 100 days after HSCT.

The study is specifically focused on the myeloablative allogeneic HSCT because of the established high risk for ARF. For the purpose of constituting a uniform patient population, patients who did not have HLA full-matched related donors (four patients) in addition to those who did not have entirely the same conditioning regimen (three patients) were excluded. Hence, a total of 39 myeloablative allogeneic HSCT patients were included after excluding 26 autologous and/or non-myeloablative HSCT patients.

To have a detailed evaluation, patients' medical histories, physical examinations, baseline laboratory testings, chest X-rays, electrocardiograms, and echocardiographies were taken and creatinine clearances were determined from urine samples collected for 24 hours. Adequate cardiac, liver, pulmonary, and renal functions were prerequisites to be accepted for HSCT. Patients were hospitalized to receive the conditioning chemotherapy regimen whenever they completed this initial evaluation.

Conditioning and HSCT procedure

All of the patients received the same conditioning regimen. None of them was treated with total body irradiation (TBI). Busulphan and cyclophosphamide were administered through a central venous catheter over 1–2 hours with doses of 3.2 and 50 mg/kg/body weight, 7 and 3 days before the infusion of the stem cells, respectively.

Cyclosporine and prednisolone were used together in all patients for the prophylaxis against GVHD.

Prophylaxis was administered against *Pneumocystis carinii*, fungal infections, and cytomegalovirus with trimethoprim-sulfamethoxazole, fluconazole, and acyclovir, respectively.

The sources of donor hematopoietic cells were granulocyte colony-stimulating factor-stimulated peripheral blood hematopoietic cells in all patients. The amount of collected CD34⁺ hematopoietic stem cells was determined by enumeration using a single-platform assay, ProCOUNTTM (Becton Dickinson Biosciences, San Jose, CA, USA) in which the absolute number of CD34⁺ cells is directly derived from a single flow cytometric measurement. The above-mentioned technique for CD34⁺ cell enumeration is described in detail elsewhere.¹⁰ Finally, the collected donor hematopoietic stem cells were infused on day "zero" and all consequent days were numbered starting from that day on.

Patient monitoring

Patients were regularly assessed during their hospital stay for complications, predisposing to acute renal injury, including hypotension (defined as systolic blood pressure <90 mmHg), sepsis (defined by positive blood cultures indicating bacteremia or fungemia), and organ toxicities. All patients were monitored for signs and symptoms of GVHD and hepatic veno-occlusive disease. Total serum bilirubin, cyclosporine levels, serum albumin, blood urea nitrogen, and serum creatinine were measured on days 7, 14, 21, 30, 60, and 100. To measure cyclosporine blood concentration, a sample of venous blood was drawn 2 hours after the cyclosporine dose was given. All medications were recorded and analyzed separately in terms of their risk for nephrotoxicity. Hepatic veno-occlusive disease was defined as finding of at least twofold increases in total bilirubin levels and transaminases with ascites.¹¹

ARF was defined as a twofold rise in serum creatinine concentration of baseline value or a >50% decrease in creatinine clearance. Patients who developed acute kidney injury (AKI) were divided into three categories as given in Table 1.

Urine microprotein/creatinine ratio was assessed in each patient to evaluate proteinuria. Urine samples for this process were provided from urine collected for 24 hours for creatinine clearance measurement.

Statistical analysis

SPSS 11.0 software was used for the statistical analysis and the Kolmogorov–Smirnov test to determine the normality of the distributions of variables. Continuous variables with normal distribution are presented as mean ± SD. Median value is used where normal distribution is absent. Statistical analysis for the parametric variables was performed using the Student's *t*-test between the two groups. The Mann–Whitney *U*-test

TABLE 1. Classification of ARF.

Stage	
I	Increased serum creatinine $\times 2$ or GFR ^a decrease $> 50\%$
II	Increased serum creatinine $\times 3$ or GFR decrease $> 75\%$ or serum creatinine > 4 mg/dL
III	Stage II and requiring dialysis

Note: ARF, acute renal failure.

^aGFR determined by estimating creatinine clearance from 24-hour urine collections.

was used to compare non-parametric variables between the two groups. Qualitative variables were given as percentages and the correlation between categorical variables was investigated using the chi-square test. A p -value of <0.05 was considered to be significant.

RESULTS

Baseline characteristics of 39 allogeneic HSCT patients are summarized in Table 2. The mean age of the 39 patients was 30.97 ± 12.33 years; 24 of the 39 patients were male. Acute myeloid leukemia and acute

TABLE 2. Baseline characteristics of the allogeneic HSCT patients ($n = 39$).

Characteristics	Values
Age (year)	30.97 ± 12.33
Male/female, n (%)	24 (61.5)/15 (38.5)
Diagnosis, n (%)	
Acute myeloid leukemia	27 (69.2)
Acute lymphoblastic leukemia	7 (17.9)
Non-Hodgkin's lymphoma	3 (7.7)
Myelofibrosis	1 (2.6)
Myelodysplastic syndrome	1 (2.6)
Hemoglobin level (g/dL) ^a	11.06 ± 2.81
White blood cell count (mm^3) ^a	4317 ± 2548
Platelet count (mm^3) ^a	153769 ± 91285
CD34 ⁺ cell count ($\times 10^6/\text{kg}$) ^a	6.54 ± 1.72
Serum creatinine level (mg/dL) ^a	0.71 ± 0.19
Creatinine clearance ($\text{mL}/\text{min}/1.73 \text{ m}^2$) ^a	133.03 ± 44.54
Serum albumin level (g/dL) ^a	3.72 ± 0.38
24-Hour urine volume (mL/day) ^a	2311 ± 1122
Amount of proteinuria (mg/day) ^a	224 ± 148

Note: HSCT, hematopoietic stem cell transplantation.

^aData expressed as mean \pm SD.

lymphoblastic leukemia were the most frequent primary hematologic diseases. Baseline mean serum creatinine level and baseline mean creatinine clearance of the 39 patients were 0.71 ± 0.19 mg/dL and 133.03 ± 44.54 mL/min/ 1.73 m^2 , respectively.

None of the patients developed symptomatic hypovolemia due to vomiting and diarrhea because of extensive toxicity of myeloablative regimens during the 100 days of the study period.

ARF developed in 20 (51.3%) of the 39 patients. Out of the 20 patients, 11 (55.0%) and 9 (45.0%) developed stage I and stage II ARF, respectively. On the contrary, no patient developed stage III ARF. ARF developed in 12 (60.0%) patients within the first 2 weeks and in 8 (40.0%) patients within 2–4 weeks. No patient developed hepatic veno-occlusive disease, thrombotic microangiopathy, or TLS.

Comparison of demographic, clinical, and biochemical parameters in patients with and without ARF is summarized in Table 3. Serum creatinine levels at the second and third weeks and first and second months were significantly higher in patients with ARF than in controls (p : 0.022, 0.003, 0.001, and 0.001, respectively) (Figure 1). The values of creatinine clearance at the third week and first and second months were meaningfully lower in ARF group compared to the control group (p : 0.003, 0.027, and 0.003, respectively) (Figure 1).

Body surface area was higher in ARF group than in controls (p : 0.046). Basal hemoglobin level was higher in ARF group when compared to controls (p : 0.007). On the contrary, there was no significant difference between the two groups in terms of age, gender, primary hematologic disease, engraftment period, presence of GVHD, clinical response after allogeneic HSCT, presence of sepsis, presence of coexistent disease, use of amphotericin-B and vancomycin, CD34⁺ cell count per kilogram of body weight, cyclosporine level, serum albumin level, serum hemoglobin level, white blood cell (WBC) count, platelet count, amount of proteinuria, and 24-hour urine volume ($p > 0.05$).

Demographic, clinical, and biochemical parameters in patients with stage I ARF or stage II ARF are given in Table 4. When patients with ARF were evaluated with regard to the clinical response to allogeneic HSCT, all patients with stage II ARF and four of the nine patients with stage I ARF were in remission. Two patients with stage I ARF gave no response to treatment whereas three of them were in partial remission.

Values of creatinine clearance at the third week and second month were significantly lower in patients with stage II ARF than in patients with stage I (p : 0.001 and 0.026, respectively). But there was no significant difference between the patients with stage I and stage II ARF for the values of creatinine clearance at basal, first week, second week, first month, and third month ($p > 0.05$).

TABLE 3. Demographic, clinical, and biochemical parameters in patients with and without ARF.

Characteristics	ARF group, <i>n</i> = 20	Control group, <i>n</i> = 19	<i>p</i> -Value
Age (year)	32.95 ± 9.62	28.89 ± 14.46	0.307
Gender, <i>n</i> (%)			0.550
Male	12 (60.0)	12 (63.2)	
Female	8 (40.0)	7 (36.8)	
Body surface area (m ²)	1.73 ± 0.15	1.62 ± 0.15	0.046*
Engraftment period (day)	15 (12–23)	14 (11–28)	0.525
Presence of			
GVHD, <i>n</i> (%)	2 (10)	4 (21.1)	0.330
Sepsis, <i>n</i> (%)	2 (10)	3 (15.8)	0.475
CD34 ⁺ cell count (×10 ⁶ /kg) ^a	6.97 ± 1.54	6.10 ± 1.82	0.116
Serum creatinine level (mg/dL) ^a			
Baseline	0.71 ± 0.18	0.72 ± 0.22	0.865
First week	0.70 ± 0.41	0.56 ± 0.15	0.166
Second week	0.86 ± 0.42	0.61 ± 0.16	0.022*
Third week	1.35 ± 0.73	0.73 ± 0.17	0.003*
First month	1.62 ± 0.65	0.87 ± 0.22	0.001*
Second month	1.46 ± 0.70	0.80 ± 0.22	0.001*
Third month	0.94 ± 0.38	0.78 ± 0.17	0.129
Creatinine clearance (mL/min/1.73 m ²) ^a			
Baseline	141.32 ± 42.80	124.30 ± 45.80	0.238
First week	121.65 ± 59.09	138.10 ± 49.29	0.448
Second week	113.25 ± 67.80	107.74 ± 42.41	0.773
Third week	40.86 ± 15.35	118.14 ± 30.82	0.003*
First month	71.26 ± 55.27	112.74 ± 35.85	0.027*
Second month	66.71 ± 28.74	111.36 ± 41.36	0.003*
Third month	95.92 ± 30.77	117.66 ± 38.98	0.109
Basal hemoglobin level (g/dL) ^a	12.21 ± 2.58	9.85 ± 2.58	0.007*
Basal WBC count (mm ³) ^a	4858 ± 2866	3747 ± 2091	0.177
Basal platelet count (mm ³) ^a	153350 ± 63884	154210 ± 115253	0.977
Basal albumin level (g/dL) ^a	3.76 ± 0.32	3.67 ± 0.43	0.463
Basal amount of proteinuria (mg/day) ^a	209 ± 158	241 ± 139	0.503
Blood cyclosporine level ^b	62.50 (20.0–2235.0)	93.7 (50.0–549.0)	0.270

Notes: ARF, acute renal failure; GVHD, graft-versus-host disease; WBC, white blood cell.

^aData given as mean ± SD.

^bData given as median values.

**p* < 0.05.

Hemoglobin level at the second week was lower in patients with stage II ARF than in those with stage I (*p*: 0.043) whereas it was higher in patients with stage II compared with those with stage I at the third month (*p*: 0.018). However, there was no difference between two groups in terms of hemoglobin levels at basal, first week, third week, first month, and second month

(*p* > 0.05). Cyclosporine level at the third week was higher in patients with stage II than in those with stage I (*p*: 0.019). However, there was no significant difference with regard to cyclosporine levels at basal, first week, second week, first, second, and third months (*p* > 0.05). There was no significant difference between the two groups in terms of age, gender, engraftment

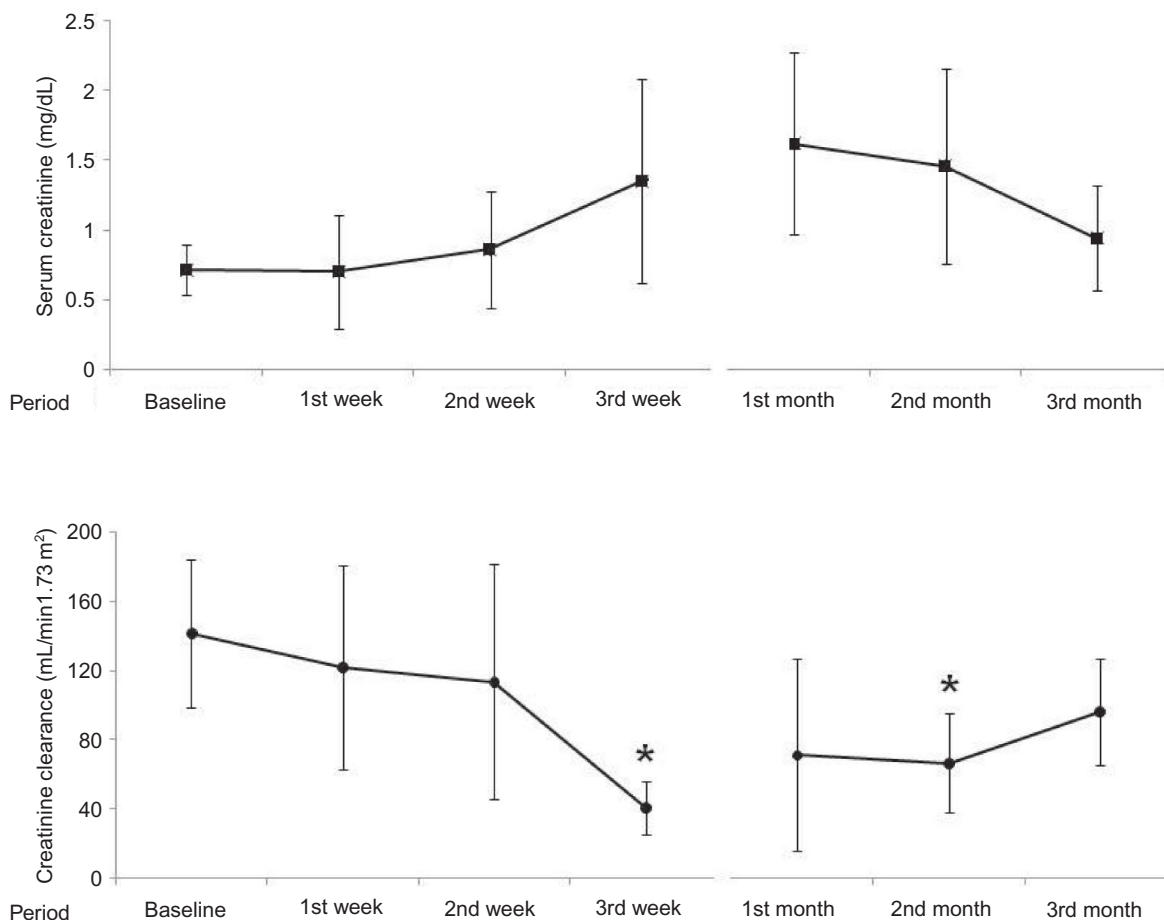


FIGURE 1. Trends of serum creatinine levels and creatinine clearance after myeloblastic HSCT. * $p < 0.05$ when compared to baseline values. 254 × 190 mm (96 × 96 DPI).

period, primary hematologic disease, body surface area, development time of ARF, presence of GVHD, presence of sepsis, presence of coexistence disease, use of amphotericin-B and vancomycin, baseline serum creatinine level, CD34⁺ cell count, serum albumin level, WBC count, platelet count, amount of proteinuria, 24-hour urine volume, and duration of ARF ($p > 0.05$).

Three patients died during the first 100 days after HSCT. One of them died on the 14th day because of neutropenic fever, gastroenteritis, and sepsis. The second patient died on the 72nd day because of pulmonary infection and pulmonary failure. Both developed ARF 7 days before death. The third patient died on the 74th day because of recurrence of primary hematological malignancy without any findings of ARF.

DISCUSSION

HSCT has become an effective treatment for some advanced malignant and non-malignant hematological malignancies. Despite many advances in immunosup-

pressive regimens and patient care, ARF remains to be a frequent complication after HSCT and leads to remarkable morbidity and mortality.¹² On the contrary, ARF is emerging as a public health problem worldwide.¹³ Despite technical improvements in dialysis and intensive care, mortality and morbidity among patients with severe ARF remain high. Several therapies, including infusion of the stem cells that can accelerate renal recovery, have been attempted in experimental models of ARF.^{14,15} Hematopoietic stem cells are recognized to have an ability to differentiate into multiple lineages of hematopoietic and non-hematopoietic tissues such as cardiac myocytes, hepatocytes, gastrointestinal epithelial cells, and vascular endothelial cells.^{16–20} Furthermore, it has been reported that adult bone marrow-derived mesenchymal stem cells or hematopoietic stem cells have a role in the recovery of the injured kidney tissues.^{5,8,21} Mechanisms underlying their healing effect are still controversial.

It was initially suggested by Zager et al. that ARF after HSCT is a very frequent and devastating complication.¹ Its incidence was first reported to be 53% by

TABLE 4. Demographic, clinical, and biochemical parameters in patients with stage I or stage II ARF.

Characteristics	Stage I ARF, <i>n</i> = 11	Stage II ARF, <i>n</i> = 9	<i>p</i> -Value
Age (year)	32.82 ± 10.98	33.11 ± 8.31	0.948
Gender, <i>n</i> (%)			0.535
Male	7 (63.6)	5 (55.6)	
Female	4 (36.4)	4 (44.4)	
Response after allogeneic HSCT, <i>n</i> (%)			0.030*
Remission	5 (45.5)	9 (100)	
Partial remission	4 (36.4)	—	
No remission	2 (18.2)	—	
Presence of			
GVDH, <i>n</i> (%)	2 (18.2)	—	0.322
Sepsis, <i>n</i> (%)	—	2 (22.2)	0.189
CD34 ⁺ cell count (×10 ⁶ /kg) ^a	7.00 ± 1.70	6.93 ± 1.42	0.929
Engraftment period (day) ^b	15 (14–23)	14 (12–16)	0.272
Serum creatinine level (mg/dL) ^a			
Baseline	0.75 ± 0.20	0.65 ± 0.13	0.232
First week	0.63 ± 0.16	0.78 ± 0.59	0.424
Second week	0.79 ± 0.37	0.95 ± 0.48	0.404
Third week	1.19 ± 0.40	1.55 ± 1.01	0.371
First month	1.48 ± 0.53	1.81 ± 0.78	0.290
Second month	1.25 ± 0.41	1.73 ± 0.91	0.195
Third month	1.07 ± 0.45	0.78 ± 0.20	0.125
Creatinine clearance (mL/min/1.73 m ²) ^a			
Baseline	137.18 ± 49.74	146.38 ± 34.71	0.645
First week	138.41 ± 61.82	102.09 ± 54.23	0.288
Second week	136.10 ± 76.38	80.61 ± 37.35	0.097
Third week	53.37 ± 8.15	28.35 ± 8.54	0.001*
First month	79.58 ± 29.63	62.94 ± 35.35	0.626
Second month	84.96 ± 24.45	51.06 ± 23.15	0.026*
Third month	100.66 ± 18.24	89.59 ± 43.72	0.527
Duration of ARF ^a	31.00 ± 11.85	26.00 ± 16.04	0.473
Hemoglobin level (g/dL) ^a			
Baseline	12.95 ± 2.90	11.31 ± 1.90	0.163
Second week	9.92 ± 2.42	7.84 ± 1.66	0.043*
Third month	9.58 ± 1.72	11.62 ± 1.49	0.018*
Basal WBC count (mm ³) ^a	5859 ± 3183	3635 ± 1945	0.084
Basal platelet count (mm ³) ^a	165090 ± 60079	139000 ± 68992	0.378
Basal albumin level (g/dL) ^a	3.80 ± 0.33	3.72 ± 0.33	0.613
Basal amount of proteinuria (mg/day) ^a	205 ± 149	213 ± 177	0.916
Cyclosporine level ^b			
Baseline	65 (20–2235)	60 (40–207)	0.918
Third week	292 (182–951)	763 (500–986)	0.019*

Notes: ARF, acute renal failure; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; WBC, white blood cell.

^aData given as mean ± SD.

^bData given as median values.

**p* < 0.05.

Zager et al., and afterward subsequent studies confirmed this unusually high incidence of ARF after HSCT.^{3,4,22,23}

The incidence of ARF was found to be 51.3% in our cohort. The first 4 weeks after HSCT seemed to have the highest risk for developing ARF in our patients in accordance with the previous reports.^{1,3,24} The overall mortality, after the first 100 days after HSCT, was 7.7%, whereas the mortality rate in patients who developed ARF was 10% in the present study. When compared to previous studies, the lower mortality rate in our study was probably related to the severity of ARF. As mentioned above, none of our patients developed dialysis requiring ARF. According to a metaanalysis, the relative risk of death after ARF in myeloablative allogeneic HSCT was greater than twofold higher than those without ARF.²⁴ However, it has been suggested that the degree of ARF after HSCT is particularly correlated with mortality.¹

It has been clarified recently that the characteristics of ARF vary among the three types of transplantations.¹² Myeloablative allogeneic HSCT carries the highest risk for ARF,^{1,4,12,22} when compared to non-myeloablative allogeneic^{24,25} and myeloablative autologous transplantations.^{1,26,27} Myeloablation requires high-dose chemotherapy with or without TBI that may cause severe vomiting, diarrhea, and renal injury. The risk for GVHD increases in myeloablative allogeneic transplantation, and GVHD may contribute to nephrotoxicity.^{28,29} Our myeloablative regimen did not include TBI, and this might have had a decreasing effect on renal injury in our patients. In addition, we did not find any significant correlation between GVHD and ARF development. Although the latter finding is in accordance with most of the previous studies,^{1,3,25} further research is needed to clarify whether there is a link between GVHD and ARF.

Patients with larger body surface area were found to be vulnerable to ARF. Although we assumed that ARF may be associated with insufficient amount of infused stem cells, we found no correlation between the number of infused stem cells per body weight and ARF development.

Calcineurin toxicity and TLS are also well-known causes for ARF. However, we did not find any correlation between blood cyclosporine levels and development of ARF. However, blood cyclosporine levels were significantly higher in patients with stage II ARF compared with patients with stage I ARF. None of our patients developed TLS in accordance with the finding that TLS in this population is reported to be quite low.² Furthermore, known risk factors such as use of amphotericin-B and sepsis did not seem to have a direct relationship with ARF development in our

patients. We conclude that high incidence of ARF in this special group of patients cannot be linked to a single cause. Rather a combination of multiple risk factors seems to be responsible for developing ARF.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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