Kidney International, Vol. 67 (2005), pp. 272–277

Acute renal failure after myeloablative hematopoietic cell transplant: Incidence and risk factors

SANGEETA R. HINGORANI, KATHERINE GUTHRIE, AMI BATCHELDER, GARY SCHOCH, NADA ABOULHOSN, JANEL MANCHION, and GEORGE B. MCDONALD

Department of Pediatrics and Medicine, University of Washington, Seattle, Washington; and Department of Clinical Research and Biostatistics, Fred Hutchinson Cancer Research Center, Seattle, Washington

Acute renal failure after myeloablative hematopoietic cell transplant: Incidence and risk factors.

Background. Survival after myeloablative therapy followed by hematopoietic cell transplant (HCT) is limited by substantial treatment-related toxicities. Acute renal failure (ARF) develops in 25% to 50% of patients after HCT.

Methods. One hundred forty-seven patients were followed prospectively from time of transplant. ARF was defined as a doubling of baseline serum creatinine at any time during the first 100 days post-transplant. We conducted a nested case-control study to identify precipitants of ARF. For each person who developed ARF, 2 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, and to types of treatment and comorbidity, 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-three patients (36%) developed ARF at a median of 33 days after transplant (range 1 to 97). Elevated risks were observed in patients who received liposomal amphotericin (OR 6.58; 95%CI 1.45–29.95) and conventional (OR 3.60; 95%CI 0.79–16.55), and in those patients with sinusoidal obstruction syndrome (SOS) (previously termed veno-occlusive disease) (OR 9.37; 95%CI 2.29–38.38). For every 0.1 mg/dL increase in baseline serum Cr, the risk of ARF decreased by 30%. Neither total body irradiation (TBI) dose, levels of metabolites of cyclophosphamide, sepsis, acute graft versus host disease (GVHD), nor cyclosporine (CSA) levels was associated with an increased risk of ARF.

Conclusion. The cumulative incidence of ARF after HCT remains high. Amphotericin use during the 2-week exposure period 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 lower risk of ARF.

Key words: acute renal failure, hematopoietic cell transplant, myeloablative conditioning therapy, risk factors.

Received for publication May 13, 2004
and in revised form July 15, 2004
Accepted for publication July 27, 2004

High-dose myeloablative therapy followed by 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 [1–4].

In 2 large retrospective reviews of patients undergoing HCT in the 1980s, the frequency of ARF (defined as a doubling of baseline serum creatinine within the first 30 days post-transplant) was 26% of 275 patients and 53% of 272 patients, respectively [1, 2]. Identified risk factors included sinusoidal obstruction syndrome, older age, jaundice, weight gain, and exposure to amphotericin B [1, 2]. In a more recent study, hepatic toxicity, sinusoidal obstruction syndrome, and lung toxicity were associated with an increased risk of ARF [4]. The conditioning regimen of cyclophosphamide and total body irradiation has also been implicated in pediatric studies [3, 5]. There is variable metabolism of cyclophosphamide between patients resulting in varying concentrations of metabolites, some of which may damage renal tubular cells in culture and deplete these cells of thymidine, a nucleotide needed for repair [6].

Since the 1980s, there have been many advances in hematopoietic cell transplantion, including more accurate human lymphocytic antigen (HLA) matching of donor and recipient, more effective strategies of infection prophylaxis, a change from the use of conventional amphotericin to liposomal formulations, and an overall reduction in the intensity of myeloablative conditioning regimens. We studied a more recent cohort of patients transplanted with allogeneic donor cells following a uniform conditioning regimen of cyclophosphamide (CY) and total body irradiation (TBI) to determine the incidence of and risk factors related to the development

of ARF. We used a nested case-control study design, in which the 14 days prior to the development of ARF was defined as the exposure period in which clinical data and time-related risk factors were ascertained.

METHODS

Between April 1997 and January 2000, all patients at the Fred Hutchinson Cancer Research Center with a hematologic malignancy undergoing allogeneic transplantation after a conditioning regimen of CY and TBI were invited to participate in this study. One hundred forty-seven patients agreed to participate, and signed informed consent forms were approved by the Institutional Review Board. The patients included in this nested case-control study were selected from the cohort of 147 patients, as described below.

Technique of hematopoietic cell transplantation

Seven days prior to the infusion of stem cells, 60 mg/kg body weight of CY was given through a central venous access catheter over 1 to 2 hours. On the following day, a second infusion of the same dose of CY was given. The pharmacokinetics of CY in this cohort of patients has been published [7]. After a day of rest, TBI (9–14.2 Gy) was administered in hyperfractionated doses from opposing cobalt sources on each of the 3 or 4 subsequent days. The kidneys were not shielded. Prophylaxis regimens against graft-versus-host disease included cyclosporine or tacrolimus and methotrexate in the majority of patients, or variations on the above, including prednisolone and BC3; BC3 is a murine antibody specific for human CD3. Donor hematopoietic cells were infused on day "zero;" by convention, all subsequent days are numbered from this day. Infection prophylaxis included fluconazole or itraconazole, acyclovir, and trimethoprim-sulfamethoxazole.

Study design

We used a nested 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 myeloablative conditioning therapy. Two 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, 53 cases and 106 control observation periods comprised the study population.

The following clinical data were collected during the 14 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 pretransplant patient characteristics for their association with ARF: age, gender, baseline serum creatinine (Cr), weight, and serum albumin, as well as transplant-related factors such as TBI dose and cyclophosphamide (CY) metabolite exposure. 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 potential risk factors.

Variations in the metabolism of CY were analyzed as areas under the curve (AUCs) as previously described [7]. AUCs for each of the metabolites of CY [O-carboxyethyl phosphoramide mustard (CEPM), deschloroethyl-cyclophosphamide (DCCY), hydroxypropyl-phosphoramide mustard (HPPM), 4-ketocyclophosphamide (KetoCY), and 4-hydroxy cyclophosphamide (HCY) [7]] were calculated based on their plasma levels. TBI was analyzed by total dose: 9 Gy, 12 Gy, and ≥13.2 Gy. During the 2-week exposure period, the mean pulse, systolic and diastolic blood pressure measurements, and change in weight from baseline to time of ARF were evaluated as predictors. Hypertension was defined in adults as 3 instances of either a systolic measurement ≥140 mm Hg or a diastolic measurement ≥90 mm Hg in the exposure period. In pediatric patients, hypertension was defined as 3 measurements ≥95th percentile for age and height as standardized and described elsewhere [8]. Fever was defined as any daily temperature ≥38 degrees Celsius. Bacteremia/fungemia was defined as the presence of at least 1 positive blood culture during the exposure period. Medications taken during the exposure period were divided into the broad categories of immunosuppression, antibiotics, diuretics, and antihypertensives, and these categories were analyzed separately. Nephrotoxic antibiotics analyzed individually included amphotericin, liposomal amphotericin (Abelcept; The Liposome Co., Princeton, NJ, USA), vancomycin, and gentamicin. Sinusoidal obstruction syndrome was defined based on the triad of hepatomegaly, weight gain, and jaundice [9]. The severity of SOS was classified as mild, moderate, or severe, based on symptom resolution and treatment required [10]. Acute GVHD was graded I-IV based on the Glucksberg classification as modified by a working group [11].

Statistical methods

The distributions of the continuous covariates in the cases and controls were compared using Wilcoxon rank sum tests. The odds ratios (OR) were calculated using conditional logistic regression models, which take into 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. All analyses were performed using SAS statistical software (Cary, NC, USA).

RESULTS

The demographic characteristics of the study cohort have been described previously [7]. All patients received allografts, the majority (70%) for CML. One hundred thirty-nine patients (95%) received hematopoietic cells derived from HLA-matched unrelated donors. The median age at transplant was 37 years with a range of 3–58 years of age. Of 147 patients, 53 (36%) developed ARF before day +100, at median day +33 (range day +1 to +97) after transplant.

Table 1 lists the median and ranges for the risk factors analyzed and modeled as continuous variables considered among cases and controls, and also shows the univariable associations between ARF and all the potential risk factors. The largest ORs were observed in patients who received either conventional or liposomal amphotericin (OR 5.87, 95% CI 2.33–14.79) in the 14-day exposure period prior to development of ARF, and in those who had a clinical diagnosis of moderate or severe SOS prior to the date of onset of ARF (OR 5.19, 95% CI 1.86–14.43). There was no difference in size of the increased risk of ARF associated with the receipt of conventional versus liposomal amphotericin (OR 5.0 vs. 5.2, respectively). The risk of ARF appeared to be substantially lower in adults than children (OR 0.21, 95% CI 0.07–0.66). The risk of ARF was also associated with a 5% greater gain in weight from baseline (initial weight at clinic visit prior to the start of cyclophosphamide) to the end of the exposure period (OR 1.37, 95% CI 1.05–1.78). Higher levels of baseline serum creatinine were associated with a reduced risk of ARF (0.83 per 0.1 mg/dL, 95% CI 0.73–0.94). Exposure to metabolites of CY during conditioning therapy was not associated with an increased risk of ARF. Similarly, higher doses of TBI and higher CSA levels did not appear to increase the risk of ARF in these patients.

Many of these factors were inter-related. For example, younger patients were more likely to receive amphotericin, and were less likely to have developed moderate or severe SOS. Those patients with the largest weight gain from baseline to the onset of ARF were more likely to have SOS and to have received amphotericin. In a multiple regression model adjusted for age and gender (Table 2), the OR for ARF associated with having received liposomal amphotericin during the 2-week exposure period was 6.5 (95% CI 1.45–29.95). Patients who received conventional amphotericin also had an increased risk of ARF (OR 3.6, 95% CI 0.79–16.55). Similarly, patients with moderate or severe SOS were more likely to develop ARF than patients without SOS or those with mild SOS (OR 9.37, 95% CI 2.29–38.38). For every 0.1 mg/dL increment in baseline serum creatinine, the OR for ARF was reduced by approximately 30% (95% CI 0.56–0.88). There was little difference in the risk of ARF between adults and children after adjusting for amphotericin use, SOS, and baseline serum creatinine (OR 0.79; 95% CI 0.14–4.40). The association between a weight gain of >5% and ARF was confounded by amphotericin use, and SOS and was not a predictor of ARF after adjusting for these factors (OR 1.13, 95% CI 0.83–1.55). Adjusted ORs for the remaining variables in Table 1 were calculated and were not appreciably different from the univariable ORs (data not shown).

DISCUSSION

Acute renal failure, defined as a doubling of baseline serum creatinine, remains common after HCT. In spite of recent advances in the care of patients undergoing HCT, the cumulative incidence of ARF was 36% in this cohort. Two major factors associated with an increased risk of the development of ARF were identified by multivariable analysis: amphotericin use and the presence of moderate or severe SOS. There was no evidence in the data that the incidence of ARF was related to TBI dose, cyclophosphamide metabolite exposure levels, sepsis, GVHD, cyclosporine levels, weight gain, and older age.

Unlike previous studies of ARF after HCT, all of our patients received the same conditioning regimen, allowing us to cleanly evaluate dosage of TBI as a risk factor. This is also the first study to investigate levels of metabolites of cyclophosphamide as potential mediators of renal injury. Though other studies have looked at any cyclosporine use, we investigated blood levels of cyclosporine in relation to the occurrence of ARF. Although much of the renal toxicity of cyclosporine is thought to be dose dependent [12], we found that higher levels of cyclosporine were not associated with an increased risk of ARF in this patient population. However, in children, cyclosporine levels above 200 μg/L have been associated with an increased risk of ARF [13].

Our data suggest that an elevated baseline serum creatinine was associated with a reduced risk. It is conceivable that this association is in part an artifact of our definition of ARF (at least a doubling of baseline serum creatinine level) because the absolute change required to meet the criterion is less for a person with a low baseline level than a higher one. However, a possible basis for this reduced risk being genuine is suggested by experimental animal data showing increased cholesterol in renal tubular cells at times of systemic stress or direct tubular injury [14, 15]. Increased levels of cholesterol in renal tubular cells confer a "cytoresistant" state potentially protecting the kidney from further injury and the development of ARF [14, 15]. This cytoresistant state can persist for a variable length of time after the initial injury [14]. Thus, to the extent that a high baseline serum creatinine reflects earlier

Table 1. Odds ratio of renal insufficiency with 95% confidence intervals

Factor	Controls	Median *range*	Cases	Median *range*	Odds ratio
Pretransplant characteristics					
Age *years*					
4–17	6		11		1.0
18–55	100		42		0.21 (0.07–0.66)
Gender					
Female	45		20		1.0
Male	61		33		1.22 (0.62–2.40)
Serum creatinine (×0.1 *mg/dL*)	106	1.0 (0.3–1.4)	53	0.9 (0.2–1.4)	0.83 (0.73–0.94)
GFR (×10 *mg/dL*)	106	86 (51–223)	53	104 (47–363)	1.16 (1.06–1.27)
Serum albumin *mg/dL*	105	4.1 (2.4–4.8)	52	4.0 (3.0–4.9)	0.47 (0.18–1.22)
TBI *Gy*					
9 or 12	49		21		1.0
13.2 or 14.4	57		32		1.31 (0.67–2.56)
AUC–CY (×100)	106	6085 (3647–8271)	53	6246 (2767–8546)	1.01 (0.98–1.04)
AUC–HCY (×100)	106	154 (59–283)	53	138 (61–298)	0.57 (0.30–1.10)
AUC–CEPM (×100)	104	379 (118–706)	53	424 (118–1881)	1.14 (0.94–1.38)
AUC–DCCY (×100)	106	470 (210–1685)	53	588 (264–1619)	1.08 (0.94–1.24)
AUC–KetoCY (×100)	106	227 (83–648)	53	211 (85–648)	1.04 (0.73–1.48)
AUC–HPPM (×100)	87	69 (14–471)	52	66 (18–1051)	1.07 (0.77–1.48)
AUC–PM (×100)	104	1013 (346–4162)	53	966 (486–7019)	1.01 (0.97–1.05)
Medications during exposure period					
Antihypertensives					
No	40		18		1.0
Yes	66		35		1.20 (0.58–2.49)
Diuretics					
No	78		32		1.0
Yes	28		21		2.22 (0.98–5.05)
Amphotericin ABLC					
No	102		43		1.0
Yes	4		10		5.00 (1.57–15.94)
Amphotericin B					
No	101		40		1.0
Yes	5		13		5.20 (1.85–14.59)
Gentamicin					
No	98		48		1.0
Yes	8		5		1.34 (0.37–4.93)
Vancomycin					
No	79		32		1.0
Yes	27		21		1.90 (0.94–3.83)
Clinical characteristics during exposure period					
Pulse (×10)	104	91 (65–118)	52	92 (73–125)	1.24 (0.93–1.65)
Hypertension					
No	53		29		1.0
Yes	53		24		0.81 (0.40–1.63)
Systolic BP (×10)	106	126 (98–146)	53	124 (97–151)	0.86 (0.63–1.17)
Diastolic BP (×10)	106	80 (51–95)	53	76 (57–96)	0.65 (0.42–1.01)
Pulse pressure (×10)	106	45 (28–69)	53	47 (32–75)	1.12 (0.76–1.66)
Fever					
No	56		28		1.0
Yes	49		25		1.03 (0.48–2.19)
High temperature (°C)	105	37 (36–39)	53	37 (36–39)	1.98 (0.98–4.01)
Total bilirubin	106	1.9 (0.4–21.6)	52	1.6 (0.5–35.2)	1.04 (0.96–1.14)
Infection					
No	92		44		1.0
Yes	14		9		1.41 (0.53–3.77)
Weight change (>5%)	105		53		1.37 (1.05–1.78)
Cyclosporine level (×100)	99	500 (131–1803)	51	422 (89–1572)	0.95 (0.86–1.04)
Clinical events before case time					
SOS					
None, mild, or other diagnosis	98		38		1.0
Moderate or severe	8		15		5.19 (1.86–14.43)
Acute GvHD					
Grade 0, I, or II	91		42		1.0
Grade III or IV	14		10		1.49 (0.60–3.70)

injury, patients with such levels would truly be at relatively low risk of ARF. However, Zager et al [2] found a high baseline serum creatinine (>0.7 mg/dL) was independently associated with the development of dialysis-requiring ARF. The differing results between this study and the present one may be secondary to the choice of baseline serum creatinine. Zager et al used serum creatinine on the day of transplant for this purpose, but this creatinine measurement may reflect changes caused by the conditioning regimen and/or hydration during the time

Table 2. Odds ratios of renal insufficiency from a multiple regression model, adjusted for age (<18 vs. ≥18 years) and gender

Factor	Odds ratio	95% CI	*P* value
Amphotericin ABLC	6.58	1.45–29.95	0.01
Amphotericin B	3.60	0.79–16.55	0.10
SOS (moderate or severe)	9.37	2.29–38.38	0.002
Serum creatinine	0.70	0.56–0.88	0.002

before transplant. Similarly, in the pediatric population, high pretransplant serum creatinine has been associated with an increased risk of renal failure in the first 3 months after transplant [16]. Differences in the findings of our study may also stem from the fact that all of our patients underwent uniform conditioning regimen and received allogeneic stem cell transplants.

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 [1, 2, 4]. In our study, the presence of SOS was associated with an increase in the risk of ARF. There is a well-known association between sinusoidal liver injury and renal insufficiency in patients after hematopoietic cell transplant [10]. It has been postulated that portal hypertension resulting from hepatic sinusoidal injury leads to both decreased renal perfusion [9] and tubular injury [17], 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 [3]. Though some have advocated keeping weight gain per se to a minimum (<10% fluid overload) to improve outcomes in this patient population [18], 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 [19–21]. 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 [21]; conditioning with TBI [22–24]; age and female gender [19]; and cyclosporine exposure [20, 25–29]. We were unable to evaluate the presence of TMA or isolate it as a risk factor for the development of ARF in our patient population because lactate dehydrogenase (LDH) levels were not routinely measured.

The finding of a sharply increased risk of ARF among patients receiving amphotericin is not surprising because the nephrotoxicity of conventional amphotericin is well known [30–33], as is its association with renal failure in the HCT population [2, 5]. What was surprising was the finding that liposomal preparations were also associated with an increased risk in this patient population. In studies conducted in febrile neutropenic patients, significantly fewer patients on liposomal amphotericin experienced nephrotoxicity (defined as doubling of baseline serum creatinine or creatinine >3.0 mg/dL) than patients on conventional amphotericin [34, 35]. In a subset analysis of the allogeneic hematopoietic cell transplant recipients, Cagnoni et al 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 [36]. In a prospective, randomized controlled trial involving non-HCT intensive care unit patients with candidal infections, Sorkine et al found that 66.7% of patients treated with conventional amphotericin experienced an increase in their serum creatinine compared to 4% of patients in the group treated with liposomal amphotericin [37]. In our study, the number of patients receiving amphotericin was small, and preferential administration of either formulation to patients otherwise at high risk of ARF could have occurred. However, we found no difference in the baseline serum creatinine between patients treated with conventional or liposomal amphotericin, in the receipt of other nephrotoxic antibiotics such as vancomycin or gentamicin, or in other indications for use. The majority of patients were placed on amphotericin, conventional or liposomal, for fever of unclear etiology, documented fungal infection, or history of fungal infection. Given the marked increase in risk of ARF in patients who received either conventional or liposomal amphotericin, we recommend that patients with fever after HCT be treated with amphotericin only if documented fungal or mold infection exists or there has been prolonged use of prophylactic triazoles. The prevalence of fungal and mold infections in our cohort was 22% and 6%, respectively. 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 but with better safety profiles [38].

CONCLUSION

This study found that ARF remains a common problem after myeloablative HCT, affecting 36% of patients. In a multivariable analysis, 2 strong risk factors were identified: use of any amphotericin formulation and the

presence of moderate or severe SOS caused by the conditioning regimen. Prevention, early recognition, and treatment of SOS, and limiting exposure to amphotericin will offer the best chance to preserve renal function in patients after HCT.

ACKNOWLEDGMENTS

We would like to thank Noel Weiss for his review of the manuscript. This research was supported by the following grants received by Dr. Hingorani: K23 NIH DK 63038 from the NIDDK at the NIH, ASN/RPA Health Scholars Grant and the NKF Young Investigators Grant and Dr. McDonald's grants: CA18029 & CA15704.

Reprint requests to Sangeeta Hingorani, M.D., MPH, Children's Hospital & Regional Medical Center, 4800 Sandpoint Way NE, Pediatric Nephrology, M1-5, Seattle, WA 98105.
E-mail: sangeeta.hingorani@seattlechildrens.org

REFERENCES

1. Gruss E, Bernis C, Tomas JF, *et al*: Acute renal failure in patients following bone marrow transplantation: Prevalence, risk factors and outcome. *Am J Nephrol* 15:473–479, 1995
2. Zager RA, O'Quigley J, Zager B, *et al*: Acute renal failure following bone marrow transplantation: A retrospective study of 272 patients. *Am J Kidney Dis* 13:210–216, 1989
3. Lane PH, Mauer SM, Blazar BR, *et al*: Outcome of dialysis for acute renal failure in pediatric bone marrow transplant patients. *Bone Marrow Transplant* 13:613–617, 1994
4. Parikh CR, McSweeney PA, Korular D, *et al*: Renal dysfunction in allogeneic hematopoietic cell transplantation. *Kidney Int* 62:566–573, 2002
5. Van Why S, Friedman A, Wei L, *et al*: Renal insufficiency after bone marrow transplantation in children. *Bone Marrow Transplant* 7:383–388, 1991
6. Mohrmann M, Ansorge S, Schmich U, *et al*: Toxicity of ifosfamide, cyclophosphamide and their metabolites in renal tubular cells in culture. *Pediatr Nephrol* 8:157–163, 1994
7. McDonald GB, Slattery JT, Bouvier ME, *et al*: Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. *Blood* 101:2043–2048, 2003
8. Bonilla-Felix M, Yetman R, Portman R: Epidemiology of hypertension, in *Pediatric Nephrology*, edited by Barrett T, Avner E, Harmon W, Baltimore, Lippincott, Williams & Wilkins, 1999, pp 959–985
9. Deleve LD, Shulman HM, McDonald GB: Toxic injury to hepatic sinusoids: Sinusoidal obstruction syndrome (venocclusive disease). *Semin Liver Dis* 22:27–41, 2002
10. McDonald GB, Hinds MS, Fisher LB, *et al*: Venocclusive disease of the liver and multiorgan failure after bone marrow transplantation: A cohort study of 355 patients. *Ann Intern Med* 118:255–267, 1993
11. Przepiorka D, Weisdorf D, Martin P, *et al*: 1994 consensus conference on acute GVHD grading. *Bone Marrow Transplant* 15:825–828, 1995
12. Atkinson K, Downs K, Ashby M: Clinical correlations with blood levels after allogeneic bone marrow transplantation: An analysis of four different assays. *Transplant Proceedings* 22:1331–1334, 1990
13. Kist-van Holthe J, Goedvolk CA, Brand R, *et al*: Prospective study of renal insufficiency after bone marrow transplantation. *Pediatr Nephrol* 17:1032–1037, 2002
14. Zager RA, Andoh T, Bennett W: Renal cholesterol accumulation: A durable response after acute and subacute renal insults. *Am J Pathol* 159:743–752, 2001
15. Zager RA, Shah V, Shah H, *et al*: The mevalonate pathway during acute tubular injury. *Am J Pathol* 161:681–692, 2002
16. Kist-van Holthe J, van Zwet J, Brand R, *et al*: Bone marrow transplantation in children: Consequences for renal function shortly after and 1 year post-BMT. *Bone Marrow Transplant* 22:559–564, 1998
17. Fink J, Cooper M, Burkhart K, *et al*: Marked enzymuria following bone marrow transplantation: A correlate of veno-occlusive disease-induced 'hepatorenal syndrome.' *J Am Soc Nephrol* 6:1655–1660, 1995
18. Michael M, Kuehnle I, Goldstein S: Fluid overload and acute renal failure in pediatric stem cell transplant patients. *Pediatr Nephrol* 19:91–95, 2004
19. Fuge R, Bird J, Fraser A, *et al*: The clinical features, risk factors and outcome of thrombotic thrombocytopenic purpura occurring after bone marrow transplantation. *Br J Hematol* 113:58–64, 2001
20. Paquette R, Tran L, Landaw E: Thrombotic microangiopathy following allogeneic bone marrow transplantation is associated with intensive graft-versus-host disease prophylaxis. *Bone Marrow Transplant* 22:351–357, 1998
21. Uderzo C, Fumagalli M, De Lorenzo P, *et al*: Impact of thrombotic thrombocytopenic purpura on leukemic children undergoing bone marrow transplantation. *Bone Marrow Transplant* 26:1005–1009, 2000
22. Lonnerholm G, Carlson K, Bratteby L, *et al*: Renal function after autologous bone marrow transplantation. *Bone Marrow Transplant* 8:129–134, 1991
23. Marshall R, Sweny P: Haemolytic-uraemic syndrome in recipients of bone marrow transplants not treated with cyclosporin A. *Histopathology* 10:953–962, 1986
24. Antignac C, Gubler M-C, Leverger G, *et al*: Delayed renal failure with extensive mesangiolysis following bone marrow transplantation. *Kidney Int* 35:1336–1344, 1989
25. Schriber J, Herzig G: Transplantation-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Semin Hematol* 42:126–133, 1997
26. Atkinson K, Biggs J, Hayes J, *et al*: Cyclosporin A associated nephrotoxicity in the first 100 days after allogeneic bone marrow transplantation: Three distinct syndromes. *Br J Hematol* 54:59–67, 1983
27. Zeigler Z, Rosenfeld C, Andrews D III, *et al*: Plasma von Willebrand factor antigen (vWF:AG) and thrombomodulin (TM) levels in adult thrombotic thrombocytopenic purpura/hemolytic uremic syndromes (TTP/HUS) and bone marrow transplant-associated thrombotic microangiopathy (BMT-TM). *Am J Hematol* 52:213–220, 1996
28. Chappell M, Keeling D, Prentice H, *et al*: Haemolytic uraemic syndrome after bone marrow transplantation: An adverse effect of total body irradiation? *Bone Marrow Transplant* 3:339–347, 1988
29. Cohen E, Lawton C, Moulder J: Bone marrow transplant nephropathy: Radiation nephritis revisited. *Nephron* 70:217–222, 1995
30. Butler W, Bennett J, Alling D: Nephrotoxicity of amphotericin B, early and late effects in 81 patients. *Ann Int Med* 61:175–187, 1964
31. Harbarth S, Burke J, Lloyd J, *et al*: Clinical and economic outcomes of conventional amphotericin B-associated nephrotoxicity. *Clin Infect Dis* 35:120–127, 2002
32. Bates D, Su L, Yu D, *et al*: Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin Infect Dis* 32:686–693, 2001
33. Wingard J, Kubilis PS, Lee L, *et al*: Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis* 29:1402–1407, 1999
34. Walsh T, Finberg R, Arndt C, *et al*: Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 340:764–771, 1999
35. Prentice H, Hann I, Herbrecht R, *et al*: A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Hematol* 98:711–718, 1997
36. Cagnoni PJ: Liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *J Antimicrob Chemother* 49:81–86, 2002
37. Sorkine P, Nagar H, Weinbroum A, *et al*: Administration of amphotericin B in lipid emulsion decreases nephrotoxicity. *Crit Care Med* 24:1311–1315, 1996
38. Marr K: Empirical antifungal therapy: New options, new tradeoffs. *N Engl J Med* 346:278–280, 2002