ASBMT American Society for Blood and Marrow Transplantation

CLINICAL RESEARCH

Chronic Kidney Dysfunction in Patients Alive without Relapse 2 Years after Allogeneic Hematopoietic Stem Cell Transplantation

Imad Abboud, Raphaël Porcher, Marie Robin, Régis Peffault de Latour, Denis Glotz, Gérard Socié, Marie-Noëlle Peraldi

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for a wide range of diseases, but is associated with a significant risk of chronic kidney disease (CKD), affecting up to 25% of survivors with a significant morbidity. The causes of CKD after HSCT vary between different studies. The present study evaluated CKD in patients undergoing allogeneic HSCT. We analyzed the clinical course of 148 patients who received allogeneic HSCT at the University Hospital of St. Louis in Paris between 1999 and 2002 and were alive after 2 years without relapse. CKD was defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, using the abbreviated modification of diet in renal disease (MDRD) equation for adults and the Schwartz formula for children. Of the 148 relapse-free 2-year survivors, 11 (7%) patients had renal dysfunction. No chronic renal failure was noted in the younger age group (<15 years at transplantation). CKD was associated with total body irradiation (TBI) (odds ratio [OR] = 4.53; 95% confidence interval [CI] 1.15 to 17.9; $P = .026$) and chronic graft-versus-host disease (cGVHD) (OR = 4.58; 95% CI 1.16-18.1; $P = .026$). Only 1 additional patient developed CKD between 2 and 5 years of follow-up (cumulative incidence of 0.7% over the 3-year period). In the CKD group, renal function tended to stabilize over the 3-year period (estimated GFR 45 ± 14 mL/min/1.73 m^2 at 2 years and 46 ± 14 mL/min/1.73 m^2 at 5 years). A 7% prevalence of CKD was noted in the relapse-free 2-year survivor patients. Renal impairement was correlated with TBI and cGVHD. Minor incidence of CKD and a relative stability of renal function were noted between 2 and 5 years after HSCT.

Biol Blood Marrow Transplant 15: 1251-1257 (2009) © 2009 American Society for Blood and Marrow Transplantation

KEY WORDS: Allogeneic hematopoietic stem cell transplantation, Chronic kidney disease, GVHD, Nephrotoxicity

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for a wide range of hematologic, neoplastic, immunologic, and metabolic diseases. It has improved the prognosis of many patients worldwide. However, many concerns rise about the long-term side effects of this therapeutic procedure. Long-term survivors represent a growing cohort, and patients older than 60 years old can today receive HSCT, increasing the risk of occurrence of cardiovascular and renal events [1,2]. Among patients who are free of disease 2 years after transplantation, the probability of living for 5 more years is 89% [3].

Chronic kidney disease (CKD) is described as relatively common, affecting around 20% of HSCT survivors [4,5]. Chronic renal failure (CRF) after successful HSCT may diminish the quality of life and may also lead to end-stage renal disease (ESRD) requiring chronic dialysis. Patients who develop ESRD after HSCT have a significantly decreased survival compared with non-HSCT patients, even when controlled for comorbidity [6].

CKD after HSCT is commonly attributed to delayed effects of the radiotherapy used in the conditioning regimen [5,7,8]. A clinical entity called "bone marrow transplantation nephropathy" was defined by the association of chronic renal impairement, anemia, and hypertension [5]. From a histologic point of view, it was compared to "radiation nephritis," with extensive mesangiolysis and severe arteriolonecrosis [9]. Previous or concurrent chemotherapy may

From the Department of Nephrology and Transplantation, St. Louis Hospital, Paris, France.
Financial disclosure: See Acknowledgments on page 1256.
Correspondence and reprint requests: Imad Abboud, MD, Department of Nephrology and Transplantation, St. Louis Hospital, 1 avenue Claude Vellefaux, Paris, France 75010 (e-mail: imad.abboud@sls.aphp.fr).
Received March 25, 2009; accepted May 26, 2009

1083-8791/09/1510-0004$36.00/0
doi:10.1016/j.bbmt.2009.05.016

potentiate the effects of radiation on the kidney. Other incriminated risk factors for CKD include nephrotoxic antimicrobials, calcineurin inhibitors (CNIs) used for the prevention and the treatment of graft-versus-host disease (GVHD), and GVHD itself [10-16].

The aim of the present study was to evaluate renal function in long-term disease-free survivors. Among 349 patients who underwent allogeneic HSCT between 1999 and 2002, we included 148 relapse-free 2-year survivors to study the CKD prevalence at 2 years after HSCT, and CKD incidence between 2 and 5 years after transplantation.

Our main objective was to identify risk factors for CKD development in long-term relapse-free survivors.

MATERIALS AND METHODS

A retrospective cohort study design was used for this study. Between January 1999 and December 2002, 349 patients underwent allogeneic HSCT at the University Hospital of St. Louis in Paris, which serves as a tertiary referral center for hematologic diseases. We analyzed the clinical course of the 148 patients who survived at least 2 years after transplantation without relapse. Data were collected from patients' charts.

Adults and children were defined using the threshold of 15 years old at the HSCT day, as in use at our institution.

Pre-HSCT Conditioning and GVH Treatments

All the 148 analyzed patients received a conditioning regimen followed by infusion of donor hematopoietic cells. Myeloablative (MA) regimens (133 patients; 90%) were typically cyclophosphamide (Cy)-based (121 patients) with either total body irradiation (TBI; 50 patients) or busulfan (Bu; 63 patients). TBI (12 Gy) was given in six fractions over 3 days. The kidneys were not shielded. Patients were considered for nonmyeloablative (NMA) HSCT if they had hematologic malignancies and were either too old or too ill to be eligible for conventional MA allogeneic HSCT. NMA conditioning regimen (15 patients; 10%) consisted of either fludarabine (Flu; 30 mg/m^2/day $\times$ 3 days) associated with low-dose TBI (2 Gy in a single fraction) or Flu (25 mg/m^2/day $\times$ 5 days) associated with Bu (4 mg/kg/day $\times$ 2 days) or Cy (60 mg/kg/day $\times$ 2 day).

Primary diagnoses are presented in Table 1. Patients were transplanted mainly for acute leukemia (41%), aplastic anemia (AA; 18%), and chronic myelogenous leukemia (CML; 15%).

Most patients received transplants from an HLA-compatible sibling (n = 106, 71%). Others received matched related (n = 5, 3%) or unrelated (n = 36, 24%) grafts, whereas only 1 patient received a graft from a monozygotic twin.

The graft was either granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs; n = 22, 15%), bone marrow (BM; n = 112, 76%), or cryopreserved umbilical cord blood (n = 14, 9%).

The day of stem cell infusion was termed "day zero," by convention.

Table 1. Primary Diseases of the 2-Year Relapse-Free Survivors (n = 148)

	Primary Diagnosis	N (%)
Malignant	Acute leukemia	61 (41%)
	Chronic myelogenous leukemia (CML)	22 (15%)
	Non-Hodgkin lymphoma	9 (6%)
	Myelodysplastic syndrome	8 (6%)
	Myeloproliferative syndrome (except CML)	5 (3%)
Nonmalignant	Aplastic anemia	27 (18%)
	Hemoglobinopathy	11 (7%)
	Other	3 (2%)
	Autoimmune diseases	1 (1%)
	Inborn errors	1 (1%)

Cyclosporine A (CsA) was given as GVHD prophylaxis in combination with a short course of intravenous (i.v.) methotrexate (MTX) in most patients. A few patients received single therapy with CsA. After 3 to 6 months the CsA level was tapered, and withdrawal was initiated between 9 and 12 months in most cases. Prolonged treatment (more than 1 year) was given to patients with chronic GVHD (cGVHD).

Diagnosis and grading of GVHD were performed according to established criteria [17].

GVHD treatment typically consisted of methylprednisolone and resumption of CsA, if already tapered. Five patients received tacrolimus as the calcineurin inhibitor therapy.

Prophylaxis for infections included acyclovir for herpes simplex virus (HSV), trimethoprim-sulfamethoxazole to prevent *Pneumocystis jirovecii* infection, oral fluconazole for prophylaxis of candidal infection, and preemptive ganciclovir for cytomegalovirus (CMV) disease among viremic patients.

For each studied patient, the following parameters were collected:

1. *Demographic data:* age, sex, height, weight.
2. *Hematologic data*: initial hematologic disease, type of donor, conditioning regimen (radiation, cytotoxic therapy, MA versus NMA), GVHD (acute (aGVHD)/cGVHD, grade/severity, organ involvement, treatment), hepatic veno-occlusive disease (VOD) (diagnosed according to established criteria [18]).
3. *Renal data*: serum creatinine value the day of transplantation, 2 years and 5 years after HSCT.

Endpoints

CKD was defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 on at least 2 occasions after 24 months of relapse-free HSCT, in the range of days 730-1825 post-transplant. GFR was calculated using the abbreviated modification of diet in renal disease (MDRD) equation for adults [19,20]:

$$\mathrm{GFR}(\mathrm{mL/min/1.73\ m^2}) = 186 \times (\mathrm{Scr})^{-1.154} \times (\mathrm{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black}),$$

and the Schwartz formula for children [21].

The time elapsed between the 2 abnormal measurements was at least 90 days to exclude patients with transient decreases in GFR.

Statistical Analysis

Continuous variables are reported as median (interquartile range). For categoric variables the frequency of positive occurrences are given along with their corresponding percentages. Characteristics of patients with and without CKD at 2 years were compared using Fisher's exact tests. Cumulative incidence curves of CKD during follow-up between 2 and 5 years posttransplant were estimated in patients free of CKD at 2 years, with relapse and death in remission as competing events.

Reported *P*-values are 2 sided, and statistical significance threshold was considered for a value of $P < .05$. All analyses were carried out using R 2.6.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

CKD Prevalence in the Cohort

The study flow chart is described in Figure 1. We analyzed the clinical course of 148 patients alive and relapse-free 2 years after HSCT. Among them, 7 patients relapsed before 5 years of follow-up and 8 died. GFR was available before BM transplantation (BMT) and at 2 years for all patients and at 5 years for all patients except 1. The median age of the study cohort at the time of HSCT was 21 years, with a range of 40 months to 56 years. Seventy-one patients (48%) were women.

The CKD prevalence at 2 years in relapse-free survivors was 7% (11 patients). As shown in Figure 1, CKD is mainly confined to adult population.

Renal Dysfunction at 2 Years

Among the 11 patients with renal impairment at 2 years, estimated GFR was 44 ± 14 mL/min/1.73 m^2. No patient had a GFR <60 mL/min/1.73 m^2 before HSCT. The median time to development of CKD was 8 months (2-20 months) posttransplantation. One patient suffered hepatic VOD with concomitant renal impairment. Another patient relapsed between 2 and 5 years after transplantation. None of the patients needed long-term dialysis nor received a renal transplant. Three patients recovered a GFR above 60 mL/min/1.73 m^2 at 5 years. This renal function improvement occurred a long time after CsA withdrawal in the vast majority of patients, suggesting that it was independent of CNI-induced vasoconstriction. In the remaining patients, GFR had recovered slightly after 2 years and remained stable thereafter. Estimated GFR was 46 ± 14 mL/min/1.73 m^2 at 5 years for the 11 patients.

In the 11 patients with CKD, 5 patients had mild hypertension, and urine protein/urine creatinin ratio ranged from 0.04 to 0.58, demonstrating low-grade proteinuria. None of the urine samples showed evidence of hematuria and none of the patients in this cohort had a renal biopsy for evaluation of CKD during the study period.

Renal functions were studied in 4 patients and showed a mainly tubular dysfunction profile comprising a low-molecular weight proteinuria, without a significant albuminuria. Mean GFR was 49 mL/min/1.73 m^2 when measured by Cr-EDTA renal clearance.

Renal Dysfunction between 2 and 5 Years after HSCT

Among patients with no CKD at 2 years (Figure 2), only 1 patient had CKD appearing between 2 and 5 years after HSCT, corresponding to a cumulative incidence (CIF) of 0.7% over the 3-year period

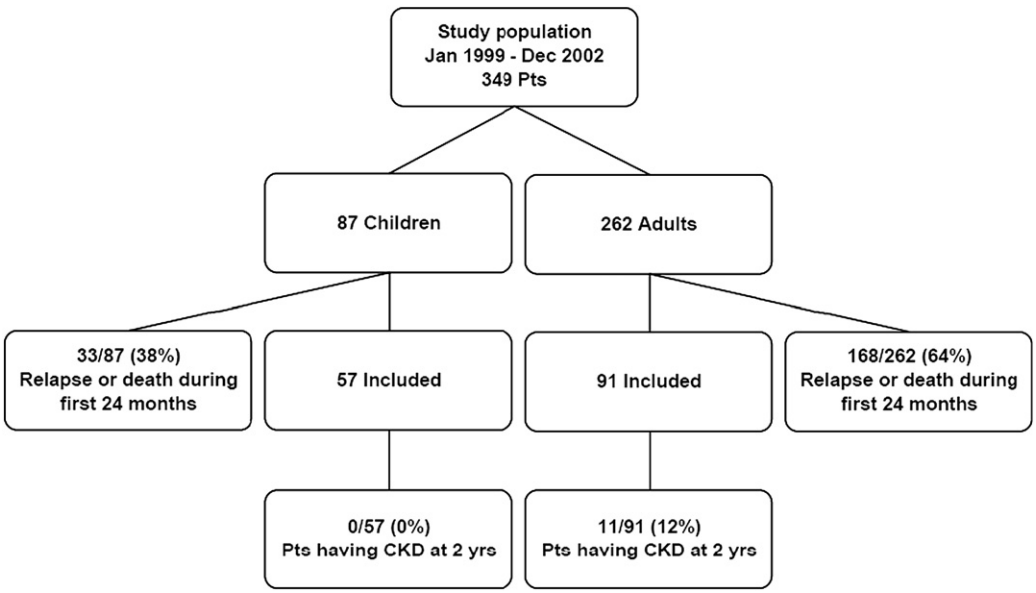

Figure 1. Study flow-chart.

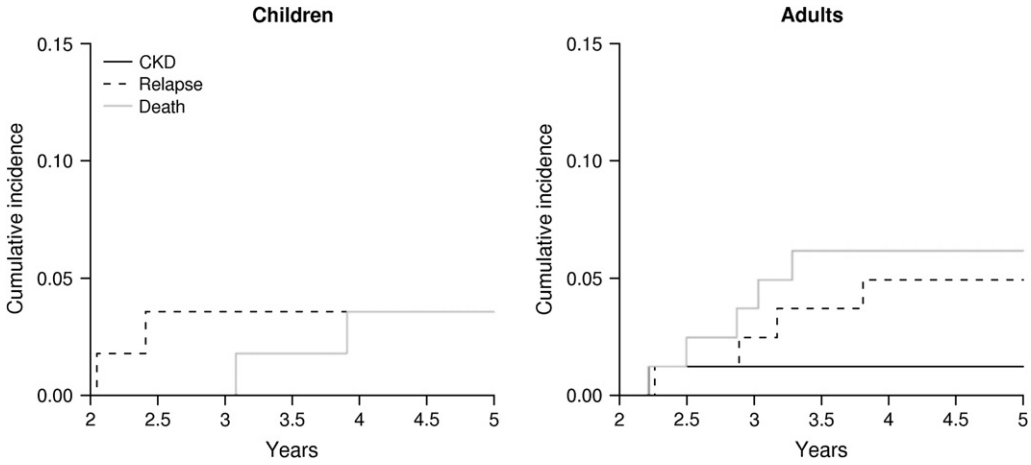

Figure 2. Cumulative incidence of chronic kidney disease (CKD), relapse, and death between 2 and 5 years of follow-up in patients alive, relapse-free, and CKD-free at 2 years (n = 137).

(95% confidence interval [CI] 0.0-2.2), 6 patients relapsed before 5 years (CIF 4.4% [95% CI 0.9-7.8]), and 7 patients died free of relapse (CIF 5.1% [95% CI 1.4-8.8]).

GFR evolution over the 5 years, in patients alive 5 years after HSCT, is shown in Figure 3.

Among 5-year survivors, median estimated GFR dropped from 107 mL/min per 1.73 m^2 before HSCT to 92 mL/min per 1.73 m^2 2 years after HSCT. After the second year, no further deterioration of kidney function occurred.

Risk Factors for CKD

The baseline characteristics and clinical course of the 2-year relapse-free survivors were categorized, based on the development of CKD, as demonstrated in Table 2.

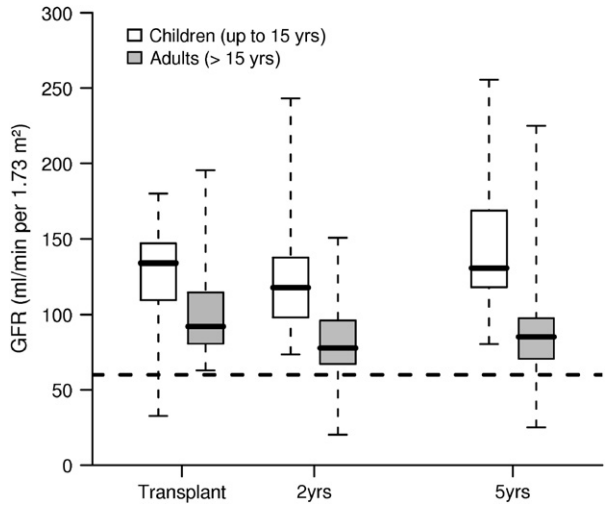

Figure 3. Glomerular filtration rate (GFR) values before HSCT, at 2 and 5 years of follow-up in patients alive at 5 years (n = 140). Box and whisker plots present the median, first (box), and third quartile of the distribution. Horizontal dashed line indicates threshold of CKD.

There was an increased risk of CKD at 2 years in patients who received TBI versus patients who did not receive TBI (P = .026), as well as in patients with a history of cGVHD (P = .026). No renal impairment was noted in the younger patients (aged <15 years at transplantation). The primary disease and the donor type were not associated with the occurence of late renal dysfunction.

Restricting analysis to adult patients only did not alter the results, although a not statistically significant association was found for cGVHD. Actually, when considering the whole sample, the odds ratios (ORs) were 4.53 (95% CI 1.15-17.9; P = .026) for TBI and 4.58 (1.16-18.1; P = .026) for cGVHD, whereas in the 92 adults only, ORs were 4.86 (1.19-19.8; P = .024) for TBI and 3.58 (0.88-14.6; P = .10) for cGVHD. ORs were thus of similar magnitude, and difference in statistical tests conclusions may be because of a loss of power with sample size reduction (92 instead of 148 patients).

DISCUSSION

Allogeneic HSCT is an increasingly recognized treatment for many diseases. More than 20,000 allogeneic HSCT procedures are performed annually around the world (about 3000 in France), with a 1-year survival rate of approximately 60% (www.ibmtr.org). In fact, this therapeutic procedure is associated with a substantial risk of death within the first 2 years after the transplantation [22,23], whereas after 2 years survival curves often reach a plateau. A previous analysis of data on 6691 patients who were disease-free 2 years after transplantation shows that such patients have an excellent prognosis [3].

The burden of CKD in the surviving patient population has significant medical and economic implications given the trend toward increasing longevity in the

Table 2. Patients Alive and Relapse Free at 2 Years: Association of Patient Characteristics with chronic Kidney Disease (CKD) at 2 Years

Variable	Median (IQR) GFR before HCT	Median (IQR) GFR at 2 years	No CKD N = 137	CKD N = 11	*P*-Value
Age					.007
≤15 years	135 (111-147)	119 (98-146)	57 (42)	0 (0)	
>15 years	92 (81-115)	78 (69-95)	80 (58)	11 (100)	
Sex					>.99
Male	119 (93-137)	102 (80-119)	71 (52)	6 (55)	
Female	94 (81-121)	83 (79-100)	66 (48)	5 (45)	
Disease					.18
Nonmalignant	115 (100-142)	95 (85-128)	42 (31)	1 (9)	
Malignant	105 (84-127)	88 (70-107)	95 (69)	10 (91)	
Transplant year					.52
1999	109 (85-126)	89 (77-104)	23 (17)	2 (18)	
2000	106 (91-133)	86 (69-117)	34 (25)	5 (45)	
2001	113 (98-126)	92 (76-107)	42 (31)	2 (18)	
2002	100 (84-141)	101 (78-128)	38 (28)	2 (18)	
Donor type					.67
Sibling	108 (85-135)	93 (74-117)	97 (72)	7 (64)	
Monozygotic twin	105	99	1 (100)	0 (0)	
Other related	114 (110-140)	107 (98-121)	5 (4)	0 (0)	
Unrelated	101 (90-122)	87 (70-98)	32 (24)	4 (36)	
Cell source					.16
BM	109 (89-132)	91 (73-111)	104 (77)	7 (64)	
CB	128 (120-149)	103 (90-146)	13 (10)	0 (0)	
PBSC	87 (76-102)	83 (65-102)	17 (13)	4 (36)	
PBSC + BM	129	133	1 (1)	0 (0)	
Conditioning regimen					>.99
Nonmyeloablative	82 (69-91)	89 (79-97)	12 (9)	1 (9)	
Myeloablative	110 (89-133)	92 (73-113)	123 (91)	10 (91)	
TBI					.026
No	107 (85-128)	93 (77-117)	85 (63)	3 (27)	
Yes	109 (90-135)	89 (69-110)	50 (37)	8 (73)	
Acute GVHD (grade)					.39
0/I	108 (88-127)	92 (73-112)	97 (72)	6 (55)	
II	106 (84-144)	89 (73-110)	33 (25)	5 (45)	
III/IV	117 (108-123)	113 (101-127)	4 (3)	0 (0)	
Chronic GVHD <2 years					.026
No	117 (92-137)	95 (79-119)	79 (63)	3 (27)	
Yes	93 (79-115)	85 (69-105)	46 (37)	8 (73)	

TBI indicates total body irradiation; GVHD, graft-versus-host disease; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood, GFR, glomerular filtration rate; CKD, chronic kidney disease; HSC, hematopoietic stem cell; IQR, interquartile range.

overall recipients of HSCT. CKD is a well-established risk factor for cardiovascular events and end-stage renal disease.

Renal complications are well described in the early period after HSCT (first 2 years). Relatively few publications were interested in the long-term renal outcome after allogeneic HSCT [24,25], with a median follow-up generally not exceeding 2 years [12-14,26,27].

The present study evaluates chronic renal impairment after allogeneic HSCT, unlike other studies, exclusively in patients alive without relapse 2 years after transplantation, that is, the real long-term survivors. We did not evaluate patients with autologous HSCT, because autologous and allogeneic HSCT should be considered as substantially different entities in the terms of nephrotoxicity risks.

Our study shows only a 7% prevalence of CKD at 2 years after HSCT in relapse-free survivors. It is difficult to compare this finding to results of other studies that dealt with incidence of CKD after HSCT, that is, taking into account cases of CRF in patients who died within 2 years after transplantation. The comparison is also hampered by the fact that many previous publications studied a cohort of either auto and allografted patients [13,28].

In addition, many other studies used a Kaplan-Meier-based statistical description, which may give an artefactually higher incidence of CKD when comparing with the cumulative incidence method [29].

Kersting et al. [24] reported in 6-month survivors a 14% to 23% cumulative incidence of CKD at 2 years (27% at 10 years) after MA and NMA [30] allogeneic HSCT. They identified the following risk factors for CKD: female sex, older age, and lower GFR pretransplant. Choi et al. [25] showed a 4.4% cumulative incidence of CKD at 5 years after HSCT in 1-year survivors. We postulate that the differences in prevalence between studies may be partially explained by several factors.

The first factor reflects variable population characteristics (age, ethnicity, genetic predisposition, environmental exposition, and underlying disease) [13,14,24,27,28,31].

The second factor is the period of follow-up. Another important point could relate to a different use of CNI. Trough levels of CsA, as well as treatment duration are rarely described in the different studies about CKD after HSCT.

Finally, a lower recently reported incidence of chronic renal disease after HSCT today may be because of general improvement in patient monitoring and management.

Another relevant point in our study is the stable kidney function between 2 and 5 years after allogeneic HSCT. This information is in agreement with previous studies [28,31,32].

Chronic renal insufficiency following HSCT in children as well as in adults has predominantly been associated with TBI [4,5,9-11,31,33-36]. This is in accordance with our findings. A dose-effect relationship has been shown in adult patients receiving TBI with higher degrees of renal shielding, resulting in significantly lower rates of BMT nephropathy [37,38].

We were not able to reproduce the same observation in the present study because the vast majority of our patients received the same radiation protocol and no patient had renal shielding.

Noteworthy, many studies reported high incidences of CKD after NMA HSCT [26,30] (from 20% to 66%, depending on the used definition criteria [14]), although using a low dose of TBI. This apparent discrepancy with the observation of TBI dose-nephropathy relationship is probably explained by other renal risk factors in this selected population (age, comorbidities, etc.), as stated by Weiss et al. [14]. The latter series mainly included early renal failure (1-year follow-up) and mixed aGVHD and cGVHD.

In accordance with many other reports in the literature [11,13,14,26], we found that cGVHD is associated with CKD. Miralbell et al. [11] observed a direct association between the presence of GVHD and treatment intensity with potentially nephrotoxic drugs, thus implying that renal dysfunction might be related to nephrotoxic drug administration, but not directly to GVHD status. However, a specific allogeneic-induced renal disease cannot be excluded, especially in light of many publications on GVHD-associated glomerulopathies [39,40].

CNIs are the cornerstone of therapy for GVHD. We think that CNI levels are higly variable and their use is often discontinuous, making it very difficult to precisely quantify organ exposure to these nephrotoxic drugs. In addition, CNI long-term use after allogeneic HSCT is mainly confined to cGVHD patients. Thus, long-term use of calcineurin inhibitors and cGVHD were not considered as separate variables in our analysis.

The results of our study should be interpreted with the following limitations in mind.

First, the study size is relatively small, with data from a single center. Second, data were collected by chart review. Third, we did not have data on urine characteristics such as protein excretion for many patients, and no kidney biopsy was available to further help understand the type and etiology of CKD.

In summary, this study describes the occurrence of CKD after allogeneic HSCT in 2 years relapse-free survivors and supports conclusions from previous studies that TBI and GVHD influence the development of CKD after HSCT.

Chronic renal insufficiency following BMT remains a great challenge facing the nephrology and oncology community today. Future long-term follow-up studies with better characterization of renal parameters will be needed.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

REFERENCES

1. Tichelli A, Bucher C, Rovo A, et al. Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. *Blood*. 2007;110:3463-3471.
2. Socie G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood*. 2003;101:3373-3385.
3. Socie G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med*. 1999;341:14-21.
4. Lawton CA, Cohen EP, Barber-Derus SW, et al. Late renal dysfunction in adult survivors of bone marrow transplantation. *Cancer*. 1991;67:2795-2800.
5. Cohen EP, Lawton CA, Moulder JE. Bone marrow transplant nephropathy: radiation nephritis revisited. *Nephron*. 1995;70:217-222.
6. Cohen EP, Piering WF, Kabler-Babbitt C, Moulder JE. End-stage renal disease (ESRD) after bone marrow transplantation: poor survival compared to other causes of ESRD. *Nephron*. 1998;79:408-412.
7. Tarbell NJ, Guinan EC, Niemeyer C, Mauch P, Sallan SE, Weinstein HJ. Late onset of renal dysfunction in survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys*. 1988;15:99-104.

8. Lawton CA, Barber-Derus SW, Murray KJ, Cohen EP, Ash RC, Moulder JE. Influence of renal shielding on the incidence of late renal dysfunction associated with T-lymphocyte deplete bone marrow transplantation in adult patients. *Int J Radiat Oncol Biol Phys*. 1992;23:681-686.
9. Antignac C, Gubler MC, Leverger G, Broyer M, Habib R. Delayed renal failure with extensive mesangiolysis following bone marrow transplantation. *Kidney Int*. 1989;35:1336-1344.
10. Van Why SK, Friedman AL, Wei LJ, Hong R. Renal insufficiency after bone marrow transplantation in children. *Bone Marrow Transplant*. 1991;7:383-388.
11. Miralbell R, Bieri S, Mermillod B, et al. Renal toxicity after allogeneic bone marrow transplantation: the combined effects of total-body irradiation and graft-versus-host disease. *J Clin Oncol*. 1996;14:579-585.
12. Miralbell R, Sancho G, Bieri S, et al. Renal insufficiency in patients with hematologic malignancies undergoing total body irradiation and bone marrow transplantation: a prospective assessment. *Int J Radiat Oncol Biol Phys*. 2004;58:809-816.
13. Hingorani S, Guthrie K, Schoch G, McDonald G. Risk factors for chronic kidney disease after hematopoietic cell transplant. *Biol Blood Marrow Transplant*. 2005;11.
14. Weiss AS, Sandmaier BM, Storer B, Storb R, McSweeney PA, Parikh CR. Chronic kidney disease following non-myeloablative hematopoietic cell transplantation. *Am J Transplant*. 2006;6: 89-94.
15. Lawton CA, Fish BL, Moulder JE. Effect of nephrotoxic drugs on the development of radiation nephropathy after bone marrow transplantation. *Int J Radiat Oncol Biol Phys*. 1994;28: 883-889.
16. Cohen EP. Renal failure after bone-marrow transplantation. *Lancet*. 2001;357:6-7.
17. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945-956.
18. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med*. 1993;118:255-267.
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999; 130:461-470.
20. Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. *Curr Opin Nephrol Hypertens*. 2001;10:785-792.
21. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am*. 1987;34: 571-590.
22. Horowitz MM, Rowlings PA. An update from the International Bone Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry on current activity in hematopoietic stem cell transplantation. *Curr Opin Hematol*. 1997;4: 395-400.
23. Armitage JO. Bone marrow transplantation. *N Engl J Med*. 1994; 330:827-838.
24. Kersting S, Hene RJ, Koomans HA, Verdonck LF. Chronic kidney disease after myeloablative allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007; 13:1169-1175.
25. Choi M, Sun CL, Kurian S, et al. Incidence and predictors of delayed chronic kidney disease in long-term survivors of hematopoietic cell transplantation. *Cancer*. 2008;113:1580-1587.
26. Hingorani S, Guthrie KA, Schoch G, Weiss NS, McDonald GB. Chronic kidney disease in long-term survivors of hematopoietic cell transplant. *Bone Marrow Transplant*. 2007;39:223-229.
27. Kist-van Holthe JE, Goedvolk CA, Brand R, et al. Prospective study of renal insufficiency after bone marrow transplantation. *Pediatr Nephrol*. 2002;17:1032-1037.
28. Gronroos MH, Bolme P, Winiarski J, Berg UB. Long-term renal function following bone marrow transplantation. *Bone Marrow Transplant*. 2007;39:717-723.
29. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res*. 2007; 13(2 Pt 1):559-565.
30. Kersting S, Verdonck LF. Chronic kidney disease after nonmyeloablative stem cell transplantation in adults. *Biol Blood Marrow Transplant*. 2008;14:403-408.
31. Frisk P, Bratteby LE, Carlson K, Lonnerholm G. Renal function after autologous bone marrow transplantation in children: a long-term prospective study. *Bone Marrow Transplant*. 2002; 29:129-136.
32. Berg U, Bolme P. Renal function in children following bone marrow transplantation. *Transplant Proc*. 1989;21(1 Pt 3): 3092-3094.
33. Tarbell NJ, Guinan EC, Chin L, Mauch P, Weinstein HJ. Renal insufficiency after total body irradiation for pediatric bone marrow transplantation. *Radiother Oncol*. 1990;18(Suppl 1):139-142.
34. Bergstein J, Andreoli SP, Provisor AJ, Yum M. Radiation nephritis following total-body irradiation and cyclophosphamide in preparation for bone marrow transplantation. *Transplantation*. 1986;41:63-66.
35. Leblond V, Sutton L, Jacquiaud C, et al. Evaluation of renal function in 60 long-term survivors of bone marrow transplantation. *J Am Soc Nephrol*. 1995;6:1661-1665.
36. Lonnerholm G, Carlson K, Bratteby LE, et al. Renal function after autologous bone marrow transplantation. *Bone Marrow Transplant*. 1991;8:129-134.
37. Lawton CA, Cohen EP, Murray KJ, et al. Long-term results of selective renal shielding in patients undergoing total body irradiation in preparation for bone marrow transplantation. *Bone Marrow Transplant*. 1997;20:1069-1074.
38. Kal HB, van Kempen-Harteveld ML. Renal dysfunction after total body irradiation: dose-effect relationship. *Int J Radiat Oncol Biol Phys*. 2006;65:1228-1232.
39. Chan GS, Lam MF, Au WY, et al. Clinicopathologic analysis of renal biopsies after haematopoietic stem cell transplantation. *Nephrology (Carlton)*. 2008;13:322-330.
40. Terrier B, Delmas Y, Hummel A, et al. Post-allogeneic haematopoietic stem cell transplantation membranous nephropathy: clinical presentation, outcome and pathogenic aspects. *Nephrol Dial Transplant*. 2007;22:1369-1376.