Kidney dysfunction after allogeneic stem cell transplantation

Sabina Kersting

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Kidney dysfunction after allogeneic stem cell transplantation

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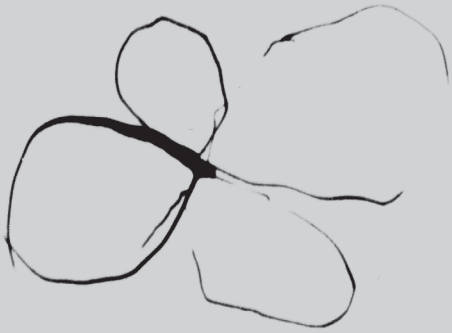
Promotor: Prof.dr. D.H. Biesma

Co-promotor: Dr. L.F. Verdonck

Voor mijn vader



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General Introduction

Allogeneic hematopoietic stem cell transplantation

Since the report in 1975 of the survival of patients with end-stage acute leukemia after bone marrow transplantation[1], the application of this treatment has grown enormously, and become a standard approach in many malignant and non-malignant hematologic diseases. The transplantation procedure consists of a conditioning regimen with chemotherapy and/or total body irradiation (TBI), followed by infusion of hematopoietic stem cells from a donor. These stem cells can be derived from peripheral blood after treating the donor with hematopoietic growth factors,[2] or from the donor's bone-marrow.[3] Since bone marrow is not the only source, the transplantation is nowadays called hematopoietic stem cell transplantation (SCT) in stead of bone marrow transplantation.

First it was believed that the success of SCT was accomplished by the myeloablative conditioning with high dose chemotherapy and high dose TBI. Later it became apparent, that the immune system plays the major role in controlling relapse of disease after SCT.[4] This was the basis for the nonmyeloablative SCT approach, where lower dose of chemotherapy and/or low dose TBI are given. The advantage of the nonmyeloablative SCT is the lower incidence of complications caused by the myeloablative strategy, which makes it possible to transplant older or sicker patients.[5]

Early complications

In the first period after SCT severe complications can occur that can lead to treatment-related mortality. The most frequently encountered problem is acute graft-versus-host disease (aGVHD). It occurs when donor T cells recognize histo-incompatibility antigens (or other proteins) on host cells. The main target organs for aGVHD are skin, gut and liver,[6] which can lead to rash, diarrhea and icterus.

Another important problem after SCT is the severely depressed immune status which leads to infectious complications. The risk for severe bacterial infections is greatest in myeloablative SCT, but fungal and viral infections, such as cytomegalovirus (CMV) reactivation, occur in both myeloablative as well as nonmyeloablative SCT recipients.[7]

A third complication that occurs only after myeloablative SCT is veno-occlusive disease (or sinusoidal occlusion syndrome). Clinically it resembles the Budd- Chiari syndrome with occlusion of the terminal hepatic venules and hepatic sinusoids. The preventive and treatment options are limited.[8]

All three complications can be accompanied by acute renal failure.[9]

SCT patients receive prophylactic therapy for GVHD and infections. Treatment with immunesuppressants, such as cyclosporine and mycophenolate mofetil, is crucial in prevention of GVHD. Treatment with ciprofloxacin, fluconazole, co-trimoxazol and valacyclovir is used to prevent infectious complications in our center. Pre-emptive treatment with gancyclovir is started in patients at the beginning of CMV reactivation detected by polymerase chain reaction of CMV DNA. These medications, especially cyclosporine, can have renal dysfunction as a side effect.[10] Acute renal failure can therefore occur in patients that suffer from complications after SCT, but also in patients without complications receiving standard medication regimens for prevention of GVHD or infections.

Late complications

Patients surviving the first period after SCT have a risk of organ related problems later in life, caused by chemotherapy, TBI, medications used, or chronic GVHD (cGVHD). In an important paper by Socie et al.,[11] late ocular effects, late pulmonary effects, late liver complications, late complications of bones and joints and late endocrine dysfunctions were reported after SCT. Surprisingly, nothing was mentioned about late kidney complications.

A distinct renal syndrome, called bone marrow transplantation nephropathy or SCT nephropathy, has been described since 1991.[12] The syndrome resembles hemolytic uremic syndrome and consists of microangiopathic anemia, accompanied by hypertension and increase in creatinine. It was recognized that it resembled radiation nephritis and with lowering of the TBI, this syndrome occurred less.[13] Since more and more patients receive nonmyeloablative SCT with low dose TBI, this syndrome becomes rare.

Chronic kidney disease in general population is considered to be a public health problem,[14] but little is known about chronic kidney disease after SCT. Because SCT recipients have received treatments that can impair renal function, it is likely that kidney dysfunction is higher than in a general population. Moreover, because kidney function declines with age and SCT patients now have better survival, progressive loss of kidney function in patients with mild renal dysfunction because of SCT may lead to kidney failure. Identification of patients with chronic kidney disease is important, because interventions might stop or slow down progression to end-stage kidney disease.[15]

Aim of this thesis

1) To study the incidence of and risk factors for acute renal failure in patients receiving myeloablative SCT and nonmyeloablative SCT and to analyze its influence on survival.
2) To study the clinical pattern of kidney dysfunction caused by SCT nephropathy.
3) To study the incidence of and risk factors for chronic kidney disease in patients receiving myeloablative SCT and nonmyeloablative SCT and to analyze its influence on survival.
4) To study the outcome of patients with renal dysfunction before nonmyeloablative SCT.

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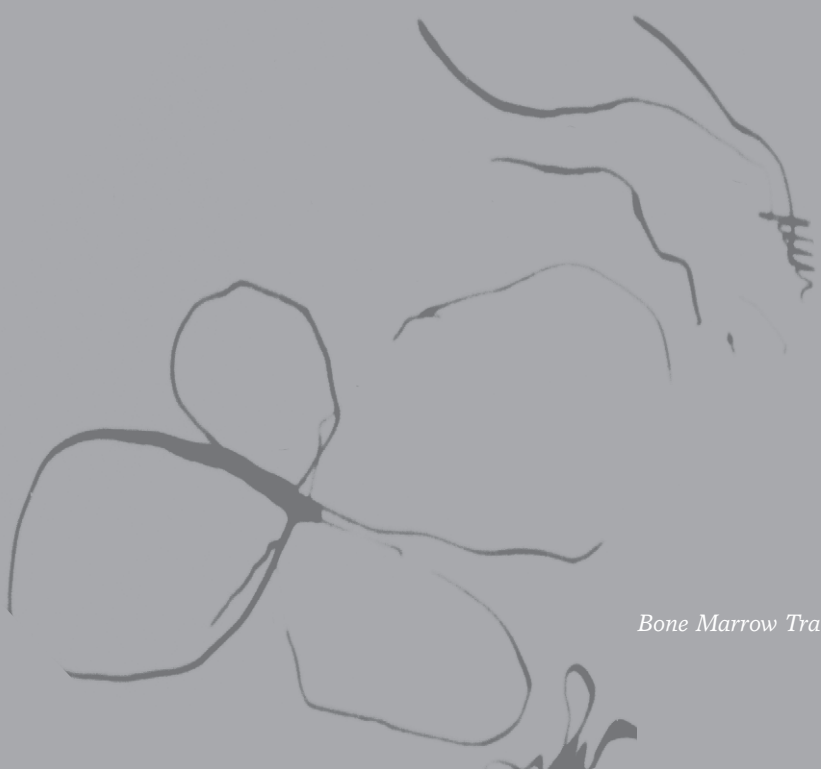
2

Acute renal failure after allogeneic myeloablative stem cell transplantation: retrospective analysis of incidence, risk factors and survival

Sabina Kersting[1], Hein A. Koomans[2], Ronald J.Hené[2], Leo F. Verdonck[1]

Departments of [1]Hematology and [2]Nephrology, University Medical Center Utrecht, The Netherlands.



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Abstract

Acute renal failure (ARF) is an important complication after stem cell transplantation (SCT). We retrospectively analyzed ARF in 363 recipients of allogeneic myeloablative SCT to identify incidence, risk factors, associated posttransplantation complications and mortality of ARF. ARF was graded as grade 0 (no ARF) to grade 3 (need for dialysis) according to creatinine, estimated glomerular filtration rate and need for dialysis. The incidence of severe renal failure (grades 2 and 3 combined) was 49.6% (180 of 363 patients). Hypertension present at SCT was identified as a risk factor for ARF ($P = 0.003$). Despite this, survival of these patients was not different compared to patients without hypertension. Admission to the intensive care unit (ICU) was a posttransplantation complication significantly associated with ARF ($P < 0.001$). Survival rate was highest in patients with ARF grade 0 - 1 and lowest in patients with grade 3 ($P < 0.001$). However, after correction for complications with high mortality (admission to the ICU, thrombotic thrombocytopenic purpura, sinusoidal occlusion syndrome, and acute graft-versus-host disease [aGVHD]) the significant difference in survival disappeared, showing that ARF without comorbid conditions has a good prognosis, and ARF with comorbid conditions has a poor prognosis. This poor prognosis is due to the presence of comorbid conditions rather than development of ARF itself.

Introduction

Complications limit the success of allogeneic stem cell transplantation (SCT). In the first months after SCT, the major complications seen are sepsis (possibly leading to organ failure and admission to the intensive care unit [ICU]),[1] sinusoidal occlusion syndrome (SOS) (also known as veno-occlusive disease),[2] thrombotic thrombocytopenic purpura (TTP),[3] acute graft-versus-host disease (aGVHD)[4] and cytomegalovirus (CMV) reactivation.[5] Several of these complications can be accompanied by acute renal failure (ARF),[2,3,6-9] and are therefore risk factors for ARF. However, ARF can also occur in the absence of these complications, mainly as a result of nephrotoxic medications, like intravenous application of amphothericine B,[8] and cyclosporine.[10] Several additional risk factors have been described for ARF, including age above 25 years[10], high risk malignancy, pulmonary toxicity and increased comorbidity score.[8] The major risk factors for ARF are not well-defined and understanding these will enable interventions that can reduce incidence and severity of ARF.

Mortality is 2-3 times higher in patients with ARF compared to patients without ARF. When ARF patients need dialysis mortality rates may rise to more than 80%, attributable to ARF.[11] Whether the higher mortality in patients with ARF is directly caused by ARF or reflects pre-existing comorbid complications, such as SOS and severe sepsis, remains unclear.[12]

The aim of this retrospective study was to identify major risk factors for ARF at the time of SCT and to identify posttransplantation complications that are associated with ARF. Second, we investigated whether the increased mortality in ARF patients is primarily due to ARF, or is influenced by other associated complications.

Patients and methods

Patients

Between January 1993 and January 2004 allogeneic myeloablative SCT was performed in 363 adult patients aged 17-57 years, at the Department of Hematology of the University Medical Center Utrecht. Patient data were collected and analyzed retrospectively using a database and computerized patient records. Patients gave informed consent and were treated according to clinical protocols approved by the local investigation review board.

SCT procedure

All patients received a myeloablative conditioning regimen that consisted of cyclophosphamide (60 mg/kg/day for 2 days), total body irradiation (TBI) (600 cGy/day for 2 days) with partial shielding of the lungs (total lung dose 850 cGy) and partial shielding of the kidneys (500 cGy/day for 2 days). After the second TBI fraction on day 0, the graft was infused. The graft was partially T cell depleted as described earlier.[13] In recipients of histocompatibility leukocyte antigen (HLA)-matched unrelated donor or a single HLA-antigen mismatched family donor, antithymocyte globulin (Rabbit ATG, Thymoglobulin™, Sangstat, Amstelveen, the Netherlands) was given before cyclophosphamide was infused.

All patients received GVHD prophylaxis with cyclosporine which started on day -2 at a dose of 3 mg/kg/day by continuous infusion for 3-4 weeks. It was thereafter given orally for 4-6 weeks at a dose that gave comparable trough levels, followed by tapering. Dose adjustments were made to keep cyclosporine trough levels between 200 ng/mL and 450 ng/mL. Serum creatinine and cyclosporine trough levels were measured at least twice a week during the first month, and at least once a week thereafter until the cyclosporine was stopped. When no active GVHD was present, cyclosporine was discontinued within 3 months after SCT. GVHD was diagnosed according to the Seattle criteria.[4] aGVHD grade I was treated with topical corticosteroids. aGVHD grade II or higher was treated with high-dose systemic corticosteroids. Limited chronic GVHD (cGVHD) was not treated and extensive cGVHD was treated with systemic corticosteroids, in some cases combined with cyclosporine.

Infection prophylaxis consisted of ciprofloxacin, fluconazole and amphotericine B given orally until granulocyte counts exceeded 500 cell/µl. Cephalotin was given intravenously from day +3 until day +13. Co-trimoxazole 480 mg twice daily and valacyclovir 500 mg twice daily were given orally from day +1 until 12 months after SCT (or longer in case of active GVHD).

Indication for dialysis in event of ARF was made by nephrologists based on the presence of hyperkaliemia and/or fluid overload. No patients were denied dialysis if an indication existed. Patients on ICU ward were treated with continuous renal replacement therapy. In other cases, intermittent dialysis was given.

Measurements

Data on patient characteristics were collected at time of SCT. Hypertension before SCT, previous autologous transplantation, gender, age, type of transplantation, mismatched transplant, underlying disease and presence of high risk malignancy were

noted for all patients. The following complications were recorded (when they occurred within 3 months after SCT): admission to ICU, aGVHD, TTP, SOS and CMV reactivation.
Serum creatinine before SCT as well as the highest serum creatinine within 3 months after SCT were noted. For these 2 values, the glomerular filtration rate (GFR) was estimated, using the MDRD formula (GFR = 186,3 x [serum creatinine]$^{-1.154}$ x age$^{-0.203}$ x [0.742 for women]).[14] We also recorded 4 cyclosporine trough levels before the highest serum creatinine and the trough level at the day of the highest serum creatinine, and calculated the mean cyclosporine trough level.

Definitions

ARF was defined as the occurrence of renal dysfunction within 3 months after SCT. ARF was graded, as described earlier,[11] as follows: grade 0 (or normal renal function) was equivalent to a decrease in estimated GFR of < 25% of the value at time of SCT. Grade 1 corresponded to a maximum of a two-fold rise in serum creatinine concentration, with a decrease in estimated GFR of > 25% of the value at time of SCT. Grade 2 corresponded to > two-fold rise in serum creatinine concentration of the value at time of SCT, without indication for dialysis. Grade 3 corresponded to patients with grade 2 parameters, and requiring dialysis.
Hypertension before SCT was defined as a documented history of hypertension, the use of antihypertensive drugs or a blood pressure > 140/90 mm Hg on the day of admission for SCT. The development of hypertension within 3 months after SCT was not an objective of this study.
Patients with acute leukemia in first complete remission, chronic myelogenous leukemia (CML) in first chronic phase and untreated severe aplastic anemia (SAA) were considered low risk; all other hematologic diseases were considered high risk.
TTP was defined as the simultaneous occurrence of thrombocytopenia and hemolytic anemia with red cell fragmentation, raised lactate dehydrogenase, raised bilirubin and decreased haptoglobin level.
SOS was defined as hyperbilirubinemia, right upper quadrant pain and weight gain within 20 days posttransplantation.

Statistics

Continuous variables are displayed as the median, with ranges in parentheses. For dichotomous variables the frequency of occurrence is given along with the corresponding percentage.

Differences between groups in characteristics at time of SCT or in complications within 3 months after SCT were assessed with the chi-square test or Fisher's exact test (where appropriate). A two-sided Student's t-test was used for continuous variables. The relative contributions of continuous and dichotomous variables on the outcome of ARF were examined using stepwise multiple logistic regressions.
Survival was analyzed by the Kaplan-Meier method. Curves were compared with the log-rank test. All P-values were two-sided and a value of < 0.05 was considered statistically significant. All analysis were performed using SPSS version 12.0 (SPSS Inc, Chicago II, USA).

Results

Occurrence of the different grades of ARF among 363 patients that underwent myeloablative SCT is depicted in Table 1. Severe ARF grade 2-3 occurred in 180 of 363 patients (49.6%) at a median of 40 days (range 7-90) after SCT (Figure 1). No difference in time of occurrence of ARF after SCT was found between January 1993 and January 2004. ARF occurred significantly earlier after SCT in patients who suffered from SOS at a median of 19 days (range 7-48) ($P < 0.001$). There was no statistical difference in timing of ARF in patients with other complications.
Univariate analysis of patient characteristics at time of SCT revealed a significantly higher proportion of patients with hypertension before SCT in patients with ARF grade 2 and grade 3 compared to grade 0 or grade 1 ($P = 0.007$). There was no statistical difference in age, gender, underlying disease, high risk disease, type of

Table 1. Occurrence of different grades of ARF

	All patients	Grade 0 ARF	Grade 1 ARF	Grade 2 ARF	Grade 3 ARF
Number of patients	363 (100%)	24 (6.6%)	159 (43.8%)	176 (48.5%)	4 (1.1%)
Creatinine before SCT (µmol/L) median (range)	65 (37-184)	69 (51-184)	66 (40-127)	63.5 (37-147)	68 (59-77)
Creatinine at ARF (µmol/L) median (range)	133 (51-1349)	83.5 (51-221)	108 (61-184)	170 (95-1349)	415 (250-706)
GFR before SCT (ml/min/1.73 m²) median (range)	112 (37-251)	107.5 (37-176)	111 (54-251)	115 (40-208)	109 (84-143)
GFR at ARF (ml/min/1.73 m²) median (range)	50 (4-158)	91.5 (30-158)	62 (34-134)	36 (4-82)	16.5 (6-26)

Abbreviations: ARF = acute renal failure; GFR = glomerular filtration rate; SCT = stem cell transplantation

transplant, mismatch transplant or creatinine and estimated GFR at time of SCT between the groups (Table 2).

Univariate analysis of complications revealed that patients with grade 2 and grade 3 ARF were more often admitted to the ICU and had a higher incidence of TTP compared to patients with grade 0 or grade 1 ARF ($P < 0.001$ and $P < 0.017$, respectively). There was no difference in the incidence of SOS, aGVHD grade 0-I, II or III-IV, and CMV reactivation in patients with grade 2 or grade 3 ARF compared to those with grade 0 or grade 1 ARF. The mean cyclosporine trough levels and the trough level at the time of the highest serum creatinine did not differ between patients with grade 0-1 ARF and patients with grade 2-3 ARF (Table 3).

Multivariate analysis of characteristics at time of SCT as well as complications within 3 months after SCT revealed that hypertension present at SCT and admission to the ICU ware significantly associated with ARF grade 2 and 3 ($P = 0.003$, odds ration [OR] 3.1 95% confidence interval [CI] 1.4-6.6 and $P < 0.001$, OR 18.4 95% CI 2.4-141.2, respectively).

Figure 1. Incidence of ARF grade 2 and 3 of 180 patients

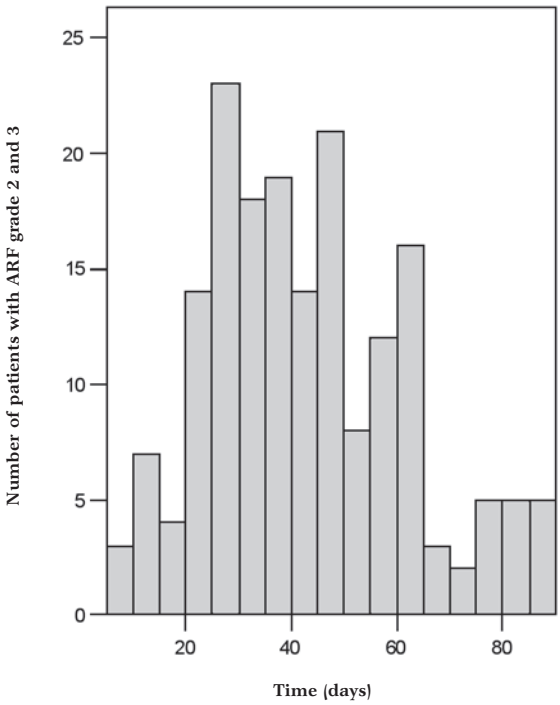


Table 2. Characteristics at time of SCT

	All patients	ARF grade 2-3	No ARF	P-value	Multivariate OR (95% CI)
Number of patients	363 (100%)	180 (49.6%)	183 (50.4%)		
Gender				ns	
Male	224 (61.7%)	108 (60%)	116 (63%)		
Female	139 (38.3%)	72 (40%)	67 (37%)		
Age median (range)	41 (17-57)	39.5 (17-57)	42 (17-57)	ns	
Younger than 40 years	176 (48.5%)	90 (50%)	86 (47%)		
Older than 40 years	187 (51.5%)	90 (50%)	97 (53%)		
History					
No history	307 (84.6%)	143 (79%)	164 (90%)		
Hypertension	35 (9.6%)	25 (14%)	10 (5%)	P=0.007	3.1 (1.4-6.6)
Autologous transplantation	21 (5.8%)	12 (7%)	9 (5%)		
Transplant				ns	
Related donor	261 (71.9%)	126 (70%)	135 (74%)		
Matched unrelated donor	102 (28.1%)	54 (30%)	48 (26%)		
Mismatch				ns	
Yes	37 (10.2%)	19 (11%)	18 (10%)		
No	326 (89.8%)	161 (89%)	165 (90%)		
Disease				ns	
AML	88 (24.2%)	42 (23%)	46 (25%)		
ALL	59 (16.3%)	28 (16%)	31 (17%)		
CML	77 (21.1%)	36 (20%)	41 (22%)		
SAA	14 (3.9%)	6 (3%)	8 (4%)		
Other	125 (34.4%)	68 (38%)	57 (31%)		
High risk				ns	
Yes	227 (62.5%)	121 (67%)	106 (58%)		
No	136 (37.5%)	59 (33%)	77 (42%)		
Creatinine before SCT (µmol/L) median (range)	65 (37-184)	64 (37-147)	66 (40-184)	ns	
GFR before SCT (ml/min/1.73 m^2) median (range)	112 (37-251)	114.5 (40-208)	111 (37-251)	ns	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; ARF = acute renal failure; CML = chronic myelogenous leukemia; GFR = glomerular filtration rate; SAA = severe aplastic anemia; SCT = stem cell transplantation

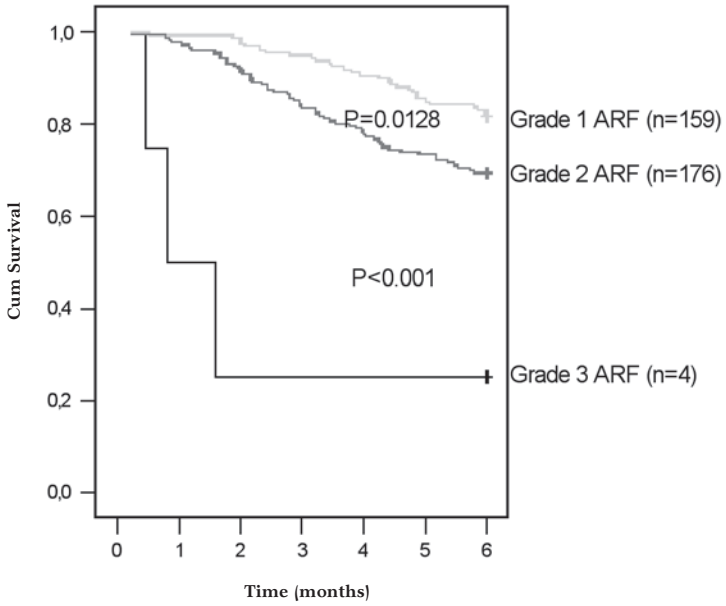
Table 3. Posttransplantation complications, cyclosporine trough levels and mortality data

	All patients	ARF grade 2-3	No ARF	P-value	Multivariate OR (95% CI)
Number of patients	363 (100%)	180 (49.6%)	183 (50.4%)		
Complications[a]				P < 0.001	
Yes	98 (27%)	64 (36%)	34 (19%)		
No	265 (73%)	116 (64%)	149 (81%)		
Acute GVHD				ns	
No-grade I	209 (57.6%)	106 (59%)	103 (56%)		
grade II	137 (37.7%)	65 (36%)	72 (39%)		
grade III-IV	17 (4.7%)	9 (5%)	8 (4%)		
SOS				ns	
Yes	16 (4.4%)	11 (6%)	5 (3%)		
No	347 (95.6%)	169 (94%)	178 (97%)		
TTP				P = 0.017	
Yes	12 (3.3%)	10 (6%)	2 (1%)		
No	351 (96.7%)	170 (94%)	181 (99%)		
ICU				P < 0.001	18.4 (2.4-141.2)
Yes	16 (4.4%)	15 (8%)	1 (1%)		
No	347 (95.6%)	165 (92%)	182 (99%)		
CMV				ns	
Yes	58 (16%)	33 (18%)	25 (14%)		
No	305 (84%)	147 (82%)	158 (86%)		
Cyclosporine trough level (ng/mL) median (range)	160 (20-850)	170 (20-850)	150 (20-520)	ns	
Alive at 6 months	272 (74.9%)	122 (68%)	150 (82%)		
Death at 6 months	91 (25.1%)	58 (32%)	33 (18%)	P = 0.002	
Mortality cause				P = 0.027	
Relapse	26 (28.6%)	12 (7%)	14 (8%)		
Complication or other cause	65 (71.4%)	46 (26%)	19 (10%)		
Complications or other cause					
SOS	4	3 (2%)	1 (1%)		
GVHD	7	5 (3%)	2 (1%)		
Infection	17	13 (7%)	4 (2%)		
CMV	4	3 (2%)	1 (1%)		
Other	33	22 (11%)	11 (6%)		

Abbreviations: ARF = acute renal failure; CMV = cytomegalovirus; GVHD = graft-versus-host disease; ICU = intensive care unit; SOS = sinusoidal occlusion syndrome; TTP = thrombotic thrombocytopenic purpura

[a] Complications: Acute GVHD III or IV, SOS, TTP, ICU, CMV reactivation

Figure 2. Survival in patients with ARF



After 6 months, 272 patients (74.9%) were still alive and 91 patients (25.1%) had died; 26 patients due to relapse (28.6%) and 65 patients due to complications (71.4%). The mortality rate was significantly higher in patients with grade 2-3 ARF compared to patients with grade 0-1 ARF (P = 0.002). There were 4 patients with grade 3 ARF. Three out of 4 patients with grade 3 ARF died shortly after start of dialysis on the ICU; 1 of refractory septic shock due to Aspergillus infection, 1 of CMV disease, and 1 of an unknown cause. The 1 patient who survived grade 3 ARF needed dialysis for 10 days because of ARF induced by non-steroidal anti-inflammatory drug (NSAID). Of the patients with a survival of less than 6 months, those with grade 2-3 ARF died significantly more often from complications than from relapse (P = 0.027) compared to patients with ARF grade 0 or grade 1 (Table 3).

There was no significant difference in cause of death between patients with or without hypertension before SCT (P = 1.00). Patients who suffered from the complications acute GVHD grade III-IV, SOS, TTP or admission to the ICU all had a significantly higher mortality rate compared to patients who suffered from CMV reactivation, or who did not have complications (Table 3).

Kaplan-Meier survival curves (Figure 2) of the 3 categories of renal failure (grade 1-3) showed significant difference in 6 months survival, with the best survival in patients with grade 1 ARF and the worst survival in patients with grade 3 ARF ($P < 0.001$). After correction for complications with high mortality (aGVHD grade III and IV, SOS, TTP, and admission to the ICU), the significant difference in 6-month survival between patients in the 3 grades of renal failure disappeared ($P = 0.240$).
At 6 months after SCT, creatinine levels were significantly higher in patients with ARF grade 2-3 compared to patients with ARF grade 0-1 ($P = 0.014$). After 12 months after SCT this difference disappeared.

Discussion

ARF after SCT is a very common complication, occurring in almost all recipients of myeloablative SCT (93.4%) in our study. This high percentage of patients with renal failure was reported in an earlier study.[11] In approximately half of the patients (49.6%) there is a severe renal failure with at least a doubling of the serum creatinine and in some cases dialysis is needed (1.1%).
A major objective of our study was to analyze whether patient characteristics at time of SCT can predict the occurrence of ARF. We found that hypertension present before SCT was the only predictor for ARF in this cohort. Although hypertension was only seen in 35 patients (9.6%) before SCT, 25 of them (71.4%) developed grade 2 or 3 ARF. There was no difference in 6-month survival or relapse rate of hematologic disease between patients with, or without, hypertension at time of SCT. Hypertension before SCT as a risk factor for ARF was not identified in previous studies.[6,10,11,15-19] Hypertension is a known risk factor for chronic kidney disease.[20] The patients with hypertension before SCT in our cohort did not have lower estimated GFRs (data not shown), so there was no apparent renal dysfunction. However, hypertension may have caused occult renal damage, which made the kidney more vulnerable to toxic medication used during and after SCT (eg cyclosporine), resulting in ARF. The underlying mechanism for hypertension as a risk factor for ARF needs further investigation. Treatment with calciumantagonist, lower dose of cyclosporine or use of alternative immunesuppressants, and pre-hydration might be helpful in decreasing the incidence of ARF in patients with hypertension. Although patients with hypertension are at risk for ARF, their prognosis at 6 months after SCT does not differ compared to patients without hypertension. In our cohort, none of the other characteristics present at time of SCT was associated with ARF. We could not therefore confirm age above 25 years or high risk malignancy as a risk factor for ARF, in contrast to the studies that found these to be risk factors.[8,10]

The first months after SCT are recognized for their association with several complications that can have a relationship with ARF,[10] and can cause increased mortality. We investigated several of these complications for their association with ARF and if complications with high mortality influenced ARF-associated survival. We found that admission to the ICU was significantly associated with the occurrence of ARF. The main reasons for SCT patients to be admitted to the ICU are respiratory failure, cardiac failure, neurological complications, gastrointestinal bleeding, and infections with associated sepsis.[21] ARF is a very common complication of SCT patients on the ICU and has been reported to be associated with sepsis and/or liver failure.[7] It is not therefore surprising that admission to the ICU was associated with ARF in this study. The second complication associated with ARF was TTP. TTP after SCT differs from classic TTP.[22] The pathogenesis of SCT-related TTP is probably dependent on endothelial injury, and ADAMTS-13 is not decreased in contrast to classic TTP. There is substantial evidence that cyclosporine plays a role in the development of SCT-related TTP.[23] In our patient cohort, 12 patients suffered from TTP, and 10 of them developed ARF grade 2-3 (Table 3). In the majority of these patients, the occurrence of ARF preceded TTP. The association between ARF and TTP may indicate a shared pathophysiological mechanism of endothelial dysfunction, which causes ARF before apparent thrombocytopenia and hemolysis occur. Cyclosporine toxicity may contributes to this endothelial dysfunction.

The median time to occurrence of ARF after SCT in our study was 40 days. This is longer than reported in other studies.[9,10,24] The one complication that was associated with a significant shorter time to occurrence of ARF after SCT was SOS. In patients suffering from SOS, ARF developed within a median of 19 days after SCT. In our study a relatively small portion of patients (4.4%) suffered from SOS compared to other studies.[6,8,10] This might explain the relative long median time to occurrence of ARF in our whole cohort compared to other studies, in which a greater number of SOS may have shortened the median time to development of ARF for all patients.

As seen in other studies, as well as ours, mortality rates during the first 6 months posttransplantation were significantly higher for patients with ARF.[11] Survival curves of three categories of ARF showed a significant difference in survival between patients with grade 1 ARF versus grade 2 and grade 3 ARF. To analyze whether the lower survival rate of grade 2 and 3 ARF was due to ARF only, or was a reflection of severe complications with a high mortality, we corrected for these complications. After this correction the difference in survival vanished and was comparable for all grades of ARF. The majority of patients with ARF did not experience one of the severe complications and these patients did not have decreased survival rates, even in the event of grade 2 ARF or the one patient with grade 3 ARF induced by use of a NSAID. Together, these data suggest that if no comorbid conditions are present,

survival rates are not influenced by ARF. The differences in survival shown in Figure 2 are thus entirely attributed to the presence of a severe complication, instead of the development of ARF per se.

The development of ARF in the absence of complications is most probably due to drug-induced nephrotoxicity. Cyclosporine is known to cause ARF. It is also known that cyclosporine trough levels do not always correlate with the occurrence of ARF.[15] There is evidence that acute cyclosporine nephrotoxicity is rapidly reversible when cyclosporine treatment is stopped. This reversibility may explain the low mortality in patients with ARF due to nephrotoxic drugs.[10] Adequate monitoring of serum creatinine is crucial in detecting drug-induced nephrotoxicity and concomitant rise of serum creatinine, to stop or adjust the dose of nephrotoxic drugs where possible.

In summary, we conclude from this retrospective study of 363 recipients of allogeneic myeloablative SCT that ARF is a very common complication. We identified hypertension present at time of SCT to be the only risk factor for occurrence of ARF after SCT. However, the prognosis at 6 months after SCT of patients with hypertension at time of SCT is similar to patients without hypertension. Complications associated with development of ARF grade 2-3 are admission to the ICU and TTP. At first sight, survival rates seem to be influenced by the degree of ARF. Grade 0 and grade 1 ARF have similar 6-month survival, whereas grade 2 ARF has significantly lower survival and grade 3 ARF has the lowest survival. However, after correction for complications with a high mortality (aGVHD grade III-IV, SOS, TTP or admission to the ICU) survival of all grades of ARF are comparable, showing that ARF without comorbid conditions has a good prognosis, and ARF with comorbid conditions has a poor prognosis. This poor prognosis is due to the presence of comorbid conditions rather than development of ARF itself.

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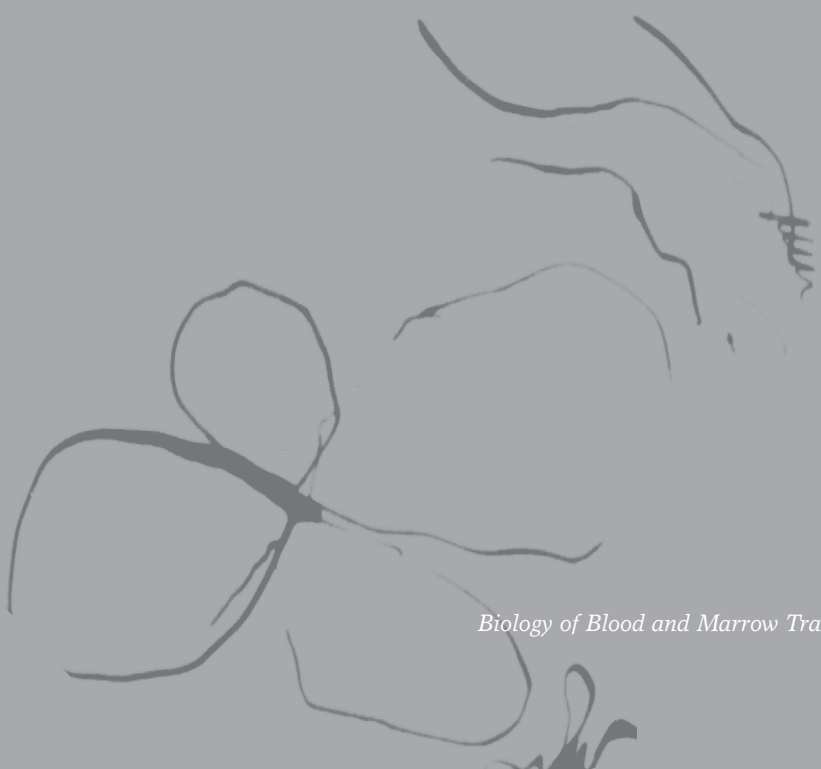
3

Acute renal failure after nonmyeloablative stem cell transplantation in adults

Sabina Kersting, Suzanne v Dorp, Matthias Theobald, Leo F. Verdonck

Department of Hematology, University Medical Center Utrecht, The Netherlands



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Abstract

Acute renal failure (ARF) after myeloablative stem cell transplantation (SCT) is a well-established problem. Little is known about ARF after nonmyeloablative SCT. The aim of the present study was to assess the incidence of ARF and to analyze risk factors for ARF. Moreover, we wanted to study whether ARF influenced survival.
We performed a retrospective cohort study of 150 adults who received nonmyeloablative SCT (fludarabine 30 mg/m^2/day for 3 days and/or total body irradiation [TBI] 200 cGy). ARF was categorized into grade 0 (no ARF), grade 1 (decrease in glomerular filtration rate > 25% and < doubling in serum creatinine), grade 2 (> doubling in serum creatinine) and grade 2 plus (> tripling in serum creatinine).
ARF grade 2-2 plus developed in 49 of 150 patients (33%) after a median of 37 days, 14 patients (9%) had ARF grade 2 plus. No patient required dialysis. Risk factors at baseline for ARF grade 2-2 plus were a history of autologous transplantation ($P = 0.008$), the absence of vascular disease ($P = 0.012$) lower serum creatinine ($P < 0.001$) and higher glomerular filtration rate (GFR) ($P < 0.001$). Acute graft-versus-host disease (aGVHD) grade III-IV was the only complication that was associated with ARF ($P = 0.035$). Overall mortality at 1 year was 23%. Patients with ARF grade 2-2 plus had significantly higher mortality compared to ARF grade 0-1 ($P = 0.006$). This was largely attributable to a diminished survival in patients with ARF grade 2 plus, who had a mortality rate of 71% caused by, among others, progression of malignancy and GVHD. This makes severe ARF an indicator for decreased survival.

Introduction

Because treatment-related morbidity and mortality (TRM) limit the success of myeloablative stem cell transplantation (SCT), a nonmyeloablative SCT regimen was developed. This regimen would be suitable for patients of older age and/or with comorbidities who were not eligible for myeloablative SCT.[1] Differences between myeloablative and nonmyeloablative conditioning are a reduction in intensities of chemotherapy and of total body irradiation (TBI) in the nonmyeloablative approach. Because patients' characteristics and transplant procedures are different in the 2 regimens, it is likely that transplant-related organ dysfunction after SCT will be different also.

Acute renal failure (ARF) after myeloablative SCT is a well-established problem. Incidence ranges from 27-82%, with need for dialysis in 1-33% of patients.[2-11]Mortality is increased in patients with ARF, with mortality ranging from 75-100% in patients who require dialysis.[2,3,5,11] ARF after myeloablative SCT is strongly associated with infectious complications and severe organ dysfunction, for example hepatotoxicity with jaundice or veno-occlusive disease (sinusoidal occlusion syndrome),[3,4,9,11] sepsis and use of amphothericine B,[9] and mechanical ventilation and admission to intensive care unit.[5,9] Older patients,[2,3] and patients with hypertension before SCT[5] have a higher risk for the development of ARF.

Because patients eligible for nonmyeloablative SCT are usually older and have more comorbid conditions,[12] ARF might occur more frequently compared to myeloablative SCT. On the other hand, because of less toxic conditioning regimens and shorter period of neutropenia, infectious complications and organ failure will occur less frequently,[13] which could have an effect on the incidence of ARF.[14]

The aim of the present study was to assess the incidence of ARF and to analyze risk factors for ARF in a large cohort. Moreover, we wanted to study whether ARF influenced survival.

Materials and Methods

Patients

Between September 1, 2001 and October 1, 2005 nonmyeloablative SCT was performed in 150 adults aged 20-69 years, at the Department of Hematology of the University Medical Center Utrecht. Patient data were collected and analyzed retrospectively using a database and patient records through December 1, 2006. Patients gave informed consent and were treated according to clinical protocols approved by the local ethics review board.

The following baseline variables were noted: sex, age, history of autologous transplantation, history of hypertension (defined as a blood pressure ≥ 140/80 mmHg or receiving antihypertensive medication), history of vascular disease (angina pectoris, myocardial infarction, cerebrovascular event and diabetes mellitus), diagnosis of hematologic disease, malignancy risk (low risk malignancy: patients with acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase and untreated severe aplastic anemia [SAA]; high risk malignancy: all other hematologic diseases), type of transplant (matched related donor, partially matched related donor, matched unrelated donor) and conditioning regimen.

Renal function was assessed according to serum creatinine concentration and estimated glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease equation defined as GFR = 186,3 x (serum creatinine)$^{-1.154}$ x age$^{-0.203}$ x (0.742 for women).[15] ARF is defined as occurrence of renal dysfunction within 100 days after SCT and categorized as follows: grade 0 (or normal renal function) is equivalent to a decrease in estimated GFR of < 25% of the value at time of SCT. Grade 1 corresponds to a < two-fold rise in serum creatinine concentration, with a decrease in estimated GFR of > 25% of the value at time of SCT. Grade 2 corresponds to > doubling in serum creatinine, without indication for dialysis. Grade 2 plus indicates > tripling in serum creatinine without indication for dialysis. Grade 3 corresponds to ARF requiering dialysis. This classification of grades of ARF is similar to other studies on ARF after SCT.[9,16,17]

The following variables posttransplantation were registered: acute graft-versus-host disease (aGVHD), cytomegalovirus (CMV) reactivation, admission to intensive care unit, hypertension and cyclosporine trough levels.

SCT procedure

The nonmyeloablative conditioning regimen consisted of fludarabine (30 mg/m^2/day for 3 days) followed by TBI of 200 cGy (n = 113) or TBI alone (n = 37). The graft was infused after TBI on day 0. In recipients of a histocompatibility leukocyte antigen (HLA)-matched unrelated donor or a single HLA-antigen mismatched family donor, antithymocyte globulin (Rabbit ATG, Thymoglobulin™, Genzyme, Cambridge. MA) was given before fludarabine was infused, at a dose of 2 mg/kg/day for 4 days (n = 60).

All patients received GVHD prophylaxis orally with cyclosporine and mycophenolate mofetil (MMF). Cyclosporine was started on day -3 at 4,5 mg/kg twice daily and continued until day +84 (n = 89) or +120 (n = 61), followed by tapering if no GVHD was present. Dose adjustments were made to keep cyclosporine trough levels

between 200 ng/mL and 400 ng/mL. Moreover, the cyclosporine dose was lowered when creatinine rise was caused by cyclosporine, at the discretion of the physician. MMF was started 5 hours after graft infusion at 45 mg/kg/day with a maximum dose of 3 g/day until day +28 (n = 89) or +84 (n = 61), followed by tapering if no GVHD was present. GVHD was diagnosed according to the Seattle criteria.[18] aGVHD grade I was treated with topical corticosteroids. aGVHD grade II or higher was treated with high-dose systemic corticosteroids.
Infection prevention consisted of ciprofloxacin and fluconazole until granulocyte counts exceeded 500 cell/µl. Co-trimoxazol 480 mg twice daily was given for 15 months and valacyclovir 500 mg twice daily was given for 12 months.

Statistical analysis

Continuous variables are displayed as the median, with range in parentheses. For non-continuous variables the frequency of occurrence are given along with the corresponding percentage. For comparison of characteristics between groups, chi-square test was used to compare proportions (or Fisher's exact test where appropriate), and two-sided Student's t-test to compare continuous outcomes.
Those parameters reaching an univariable significance level of $P \leq 0.1$ were assessed for significance using multiple logistic regressions. Kaplan-Meier survival curves were made for 1 year overall survival (OS). Curves were compared with log-rank test. All P-values were two-sided and a value of < 0.05 was considered statistically significant. All analysis was performed using SPSS version 12.0 (SPSS Inc, Chicago II, USA).

Results

ARF grade 1 (decrease in GFR > 25% and < doubling in serum creatinine) developed in 92 of 150 patients (61%) and ARF grade 2-2 plus (> doubling in serum creatinine OR > tripling in serum creatinine) developed in 49 of 150 patients (33%), with 14 patients (9%) ARF grade 2 plus. None of the patients required dialysis. ARF grade 2-2 plus developed after a median of 37 days (range 13-91).
Risk factors at baseline for ARF grade 2-2 plus were a history of autologous transplantation ($P = 0.008$), the absence of vascular disease ($P = 0.012$), lower serum creatinine ($P < 0.001$) and higher GFR ($P < 0.001$) in univariate analysis (Table 1). In multivariate analysis only the absence of vascular disease and higher GFR were risk factors for ARF (odds ratio [OR] 0.1 95% confidence interval [CI] 0.012-0.790

Table 1. Baseline risk factors, complications and outcome in patients with and without ARF

	All patients	ARF grade 2 and 2 plus	ARF grade 0 and 1	P-value	Multivariate OR (95% CI)
Sex				ns	
Male	98 (65.3%)	29 (59.2%)	69 (68.3%)		
Female	52 (34.7%)	20 (40.8%)	32 (31.7%)		
Age (range)	56.5 (20-69)	58 (20-66)	56 (20-69)	ns	
History					
Autologous	59 (39.3%)	27 (55.1%)	32 (31.7%)	P = 0.008	
Hypertension	56 (37.3%)	19 (38.8%)	37 (36.6%)	ns	
Vascular disease	17 (11.3%)	1 (2.0%)	16 (15.8%)	P = 0.012	0.1 (0.012-0.79)
Diagnosis				ns	
Acute myelogenous leukemia	26 (17.3%)	8 (16.3%)	18 (17.8%)		
Acute lymphoblastic leukemia	5 (3.3%)	3 (6.1%)	2 (2.0%)		
Chronic myelogenous leukemia	5 (3.3%)	1 (2.0%)	4 (4.0%)		
Severe aplastic anemia	6 (4.0%)	0 (0%)	6 (5.9%)		
Multiple myeloma	57 (38.0%)	22 (44.9%)	35 (34.7%)		
Non Hodgkin lymphoma	25 (16.7%)	6 (12.2%)	19 (18.8%)		
Chronic lymphatic leukemia	10 (6.7%)	3 (6.1%)	7 (6.0%)		
Myelodysplastic syndrome	8 (5.3%)	5 (10.2%)	3 (3.0%)		
Other	8 (5.3%)	1 (2.0%)	7 (6.9%)		
Risk				ns	
High risk malignancy	123 (82%)	41 (83.7%)	82 (81.2%)		
Low risk malignancy	27 (18%)	8 (16.3%)	19 (18.8%)		
Type of transplant				ns	
Matched related donor	96 (64.0%)	32 (65.3%)	64 (63.4%)		
Partially matched related donor	8 (5.3%)	2 (4.1%)	6 (5.9%)		
Matched unrelated donor	46 (30.7%)	15 (30.6%)	31 (30.7%)		
Mismatch	21 (14.0%)	6 (12.2%)	15 (14.9%)		
Conditioning				ns	
Fludarabine	1 (0.7%)	1 (2%)	0 (0%)		
Fludarabine/TBI	54 (36%)	14 (28.6%)	40 (39.6%)		
Fludarabine/TBI/ATG	58 (38.7%)	17 (34.7%)	41 (40.6%)		
TBI	37 (24.7%)	17 (34.7%)	20 (19.8%)		
Renal function					
Estimated GFR (ml/min/1.73 m²)	82 (35-187)	92 (44-187)	78 (35-142)	P < 0.001	1.0 (1.01-1.042)
Creatinine (µmol/L) median (range)	80 (46-178)	72 (46-123)	85 (57-178)	P < 0.001	
Complications					
Hypertension after SCT	42 (28.0%)	11 (22.4%)	31 (30.7%)	ns	
CMV reactivation	19 (12.7%)	8 (16.3%)	11 (10.9%)	ns	
ICU admission	6 (4%)	3 (6.1%)	3 (3%)	ns	
aGVHD grade 0-I	80 (53.3%)	22 (44.9%)	58 (57.4%)	ns	
aGVHD grade II	45 (30%)	14 (28.6%)	31 (30.7%)	ns	
aGVHD III-IV	25 (16.7%)	13 (26.5%)	12 (11.9%)	P = 0.035	
Cyclosporine trough level >400 ng/L	77 (52%)	31 (63.3%)	46 (46.5%)	ns	
Outcome					
Death at 6 months	23 (15.3%)	15 (30.6%)	8 (7.9%)	P = 0.001	
Death at 12 months	34 (22.7%)	18 (36.7%)	16 (15.8%)	P = 0.006	
Death from relapse at 12 months	18 (12.0%)	8 (16.3%)	10 (9.9%)	ns	
TRM at 12 months	16 (10.7%)	10 (20.4%)	6 (5.9%)	ns	

Abbreviations: TBI = total body irradiation; ATG = antithymocyte globulin; GFR = glomerular filtration rate; SCT = stem cell transplantation; CMV = cytomegalovirus; ICU = intensive care unit; GVHD = graft-versus-host disease; TRM = treatment-related mortality

Hypertension = tension > 140/90 mmHg;Vascular disease = angina pectoris, myocardial infarction, cerebrovascular event and diabetes mellitus; Low risk malignancy = patients with acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase and untreated severe aplastic anemia; High risk malignancy = all other hematologic diseases

and OR 1.0 95% CI 1.010-1.042). Sex, age, diagnosis, high risk malignancy, type of transplant, conditioning regimen and a history of hypertension did not differ between patients with ARF grade 2-2 plus and patients with grade 0 or 1.

aGVHD grade III-IV was the only complication occurring in the first 100 days that was associated with ARF grade 2-2 plus (P = 0.035). aGVHD 0-II, the occurrence of hypertension, CMV reactivation or admission to the intensive care unit was not associated with ARF grade 2-2 plus. Moreover, the immunesuppression regimen (cyclosporine +84 and MMF +28 or cyclosporine +120 and MMF +84) and cyclosporine trough levels (mean of all levels, level at highest creatinine, occurrence of levels ≥ 400 ng/mL) did not differ between the groups with or without ARF grade 2-2 plus. None of the patients developed thrombotic thrombocytopenic purpura or sinusoidal occlusion syndrome.

ARF in patients with ARF grade 2 plus was caused by: 1) progression of lymphoma in 3 patients, 2) severe diarrhea from GVHD grade III-IV in 5 patients, 3) nephrotoxic medication (ganciclovir and/or cyclosporine) in 4 patients, 4) multi-organ failure on the intensive care unit in 1 patients with sepsis, and 5) dehydration because of pseudomembranous colitis in 1 patient.

Figure 1. OS curves for the different grades of ARF

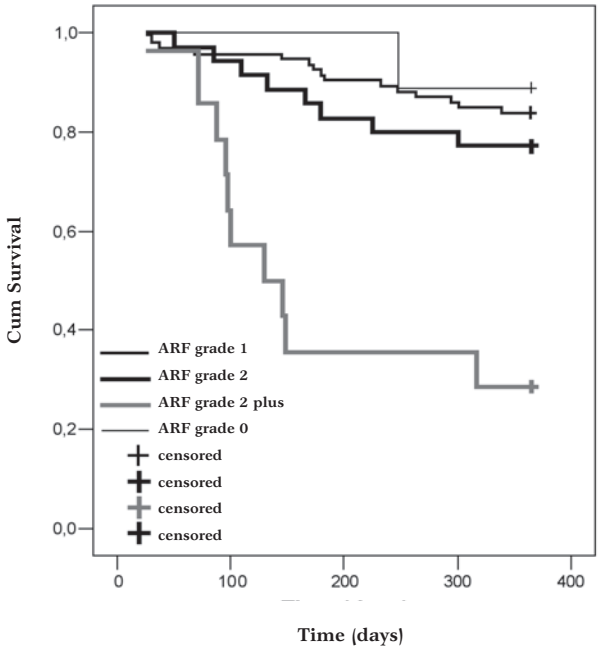


Figure 2. Kaplan-Meier survival curves for the different grades of ARF of patients with relapse of disease within 1 year (n = 23)

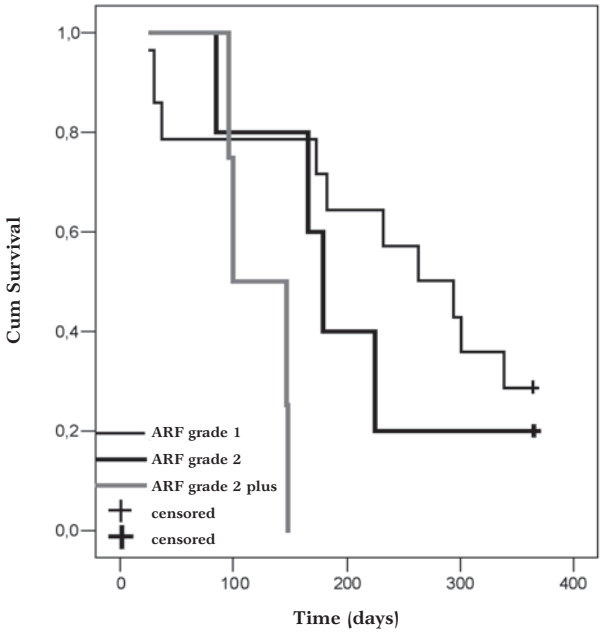
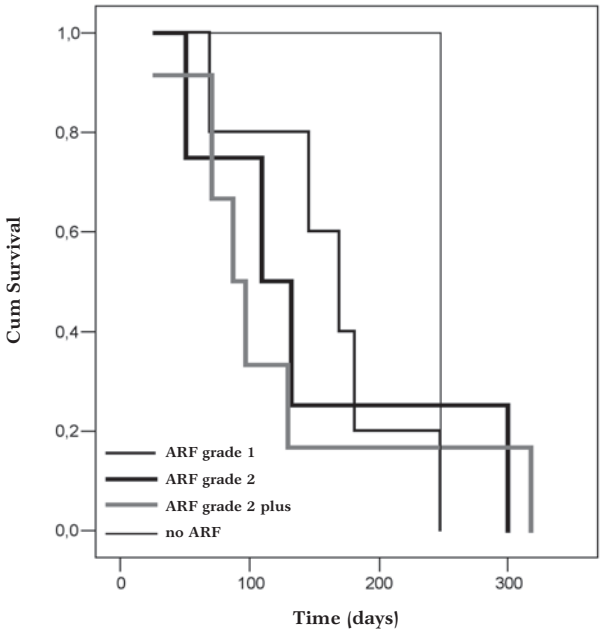


Figure 3. Kaplan-Meier mortality curves for the different grades of ARF of patients with TRM within 1 year (n = 16)



Risk factors at baseline for ARF grade 2 plus were higher GFR (P = 0.045). Complications that were associated with ARF grade 2 plus were aGVHD grade III-IV (P = 0.014) and CMV reactivation (P = 0.018). Hypertension occurred significantly less (P = 0.019) in patients with ARF grade 2 plus. These associations reflect that major causes of ARF grade 2 plus are: severe GVHD with diarrhea and dehydration which causes hypotension and risk for CMV reactivation because of treatment of GVHD with high-dose corticosteroids.

Analysis of patients without ARF (grade 0) showed significantly lower GFR and higher creatinine at baseline, opposite to patients with ARF grade 2-2 plus (data not shown).

Overall mortality at 1 year was 23%. Patients with ARF grade 2-2 plus had a significant higher mortality rate at 1 year (37%) than patients with ARF grade 0-1 (16%) (P = 0.001 and P = 0.006) (Table 1). This was largely attributable to a diminished survival in patients with ARF grade 2 plus, who had a mortality rate of 71% at 1 year. Kaplan-Meier survival curves are shown in Figure 1, with a significantly decreased OS in patients with ARF grade 2 plus compared to all other patients (P < 0.001). There was no significant survival benefit for patients without ARF (grade 0).

There was no significantly difference between TRM (n = 6) or relapse (n = 4) as cause of death for patients with ARF grade 2 plus. Of the 10 patients with ARF grade 2 plus who died, 3 died of progression of lymphoma that also caused ARF, 4 patients died of GVHD which also caused ARF, one patient died on the intensive care unit of sepsis which also caused ARF, 1 patient had a sudden death with unknown cause after recovery of ARF because of pseudomembranous colitis, and 1 patient died of relapse of AML after ARF due to cyclosporine. Relapse related mortality curves and TRM curves are shown in Figure 2 and 3. Patients with ARF grade 2 plus had a significant shorter survival after relapse compared to all other patients (P = 0.026). There was no significant difference in TRM within 1 year between the patients with the different grades of ARF.

Discussion

In this large single-center cohort of recipients of nonmyeloablative SCT, 33% of patients developed ARF grade 2-2 plus. The incidence of ARF after myeloablative SCT (conditioning with 2 days cyclofosfamide 60 mg/m^2/day and 2 days TBI of 600 cGy/day) was reported as 49% in the same center.[5] More importantly, although 14 patients (9%) developed more than tripling in serum creatinine, none of the patients required dialysis. Parikh et al.[19] found in a multicenter study on nonmyeloablative SCT an incidence of ARF and dialysis of 40% and 4% respectively, and in

a single-center study an incidence of 44% and 3% respectively.[19] This was lower compared to the myeloablative cohort.[20] In a recent small study of 26 recipients of nonmyeloablative SCT, only 19% developed ARF with 1 patient requiring dialysis.[21] This indicates that incidence of ARF after nonmyeloablative SCT is lower than after myeloablative SCT. The main reason for lower incidence of ARF is most likely the less toxic conditioning regimen and shorter neutropenia period, which diminishes the incidence of posttransplant complications and infections. In this cohort, no patient developed sinusoidal occlusion syndrome, a complication strongly associated with ARF after SCT following myeloablative conditioning,[2-4,11] or mildly reduced intensity conditioning.[21]

One of the risk factors for ARF in our study cohort was lower creatinine and a higher estimated GFR at baseline. This is in accordance with previous studies.[4,19] This is most probably affected by the definition of ARF (> doubling in serum creatinine) used in all the studies on ARF after SCT. The absolute changes required for doubling of serum creatinine is lower for persons with lower creatinine. Patients with lower creatinine will therefore meet the definition of ARF grade 2-2 plus sooner. Since serum creatinine is the most important parameter in equations for estimating GFR (both in Modification of Diet in Renal Disease equation and Cockroft and Gault equation), patients with ARF who have lower creatinine at baseline will therefore have higher GFR at baseline. Another explanation for higher incidence of ARF for patients with lower creatinine at baseline may be that the rise in serum creatinine is overlooked because serum creatinine remains in the normal range for healthy individuals.

Surprisingly, patients with vascular disease had less risk for development of ARF. A possible reason for this is prudence of the physician in monitoring cyclosporine levels and creatinine in this vulnerable patient group. Preexisting diabetes was not associated with ARF in another study.[19] This confirms that nonmyeloablative SCT is suitable for patients with diabetes not eligible for myeloablative SCT, with regard to renal function.

In our study, neither mean of all cyclosporine trough levels, level at highest creatinine, nor occurrence of levels ≥ 400 ng/mL corresponded to the development of ARF. This is remarkable, because elevated serum creatinine levels are often ascribed to cyclosporine.[1,12] Although Parikh et al.[19] did not find a correlation between cyclosporine and ARF in univariate analysis, by chart review cyclosporine appeared to be related to grade 2 ARF in almost all cases and ARF resolved with lowering of the dose.[19] Also, in our 14 patients with severe ARF, cyclosporine appeared to be the cause in 3 patients. An explanation for the discrepancy between clinical impression and statistical analysis of the effect of cyclosporine on renal function may be the

variability in cyclosporine through levels within a patient and the transient effect of cyclosporine on renal dysfunction. Also other studies failed to correlate cyclosporine to ARF.[4,5,11,19]

The only complication after SCT associated with ARF was severe aGVHD grade III or IV, which is consistent with another study.[3] However, less severe aGVHD was not a risk factor for ARF, what is in line with previous studies.[4,11,19] This makes GVHD of the kidneys less likely an explanation for the association of severe aGVHD with ARF. Dehydration because of diarrhea in patients with severe aGVHD is most likely the cause of ARF, which was seen in 5 of our patients with more than tripling of serum creatinine.

In a previous study a risk factor for ARF was hematopoietic stem cells from bone marrow compared to stem cells from peripheral blood.[19] This was, however, not confirmed in another study.[20] Because all our patients received hematopoietic stem cells from peripheral blood, we could not analyze this issue. Female sex and high risk malignancy were risk factors for ARF in 1 study,[20] but not in another,[19] and also not in our study, making it questionable whether female sex and high risk malignancies predispose for ARF.

Mortality at 1 year was more than twice as high in patients with ARF grade 2-2 plus compared to patients with ARF grade 0-1. This was largely attributable to a diminished survival in patients with ARF grade 2 plus, who had a mortality rate of 71%. Parikh et al.[19] also found significantly higher mortality in patients with ARF after SCT, but this was largely attributable to ARF that required dialysis. Mortality in patients requiring dialysis after myeloablative SCT is known to be very high.[2,3,5, 11] In our study survival was decreased in patients with ARF grade 2 plus, despite the fact that none of our patients required dialysis. Almost all ARF grade 2 plus died of conditions that also caused ARF (eg progression of lymphoma or severe aGVHD). This indicates that ARF grade 2 plus is not the cause of increased mortality, but a strong indicator for decreased survival in patients with ARF secondary to other causes.

Adequate monitoring of serum creatinine remains crucial in detecting drug-induced nephrotoxicity and to stop or adjust the dose of nephrotoxic drugs where possible. Because aGVHD grade III is a major complication associated with ARF, prevention and treatment of severe GVHD is a very important issue in diminishing the occurrence of ARF.

In conclusion, of all patients after nonmyeloablative SCT one-third will develop ARF. About 10% of patients will develop a severe ARF with high mortality caused by relapse, severe aGVHD or other complications. This makes severe ARF an indicator for decreased survival.

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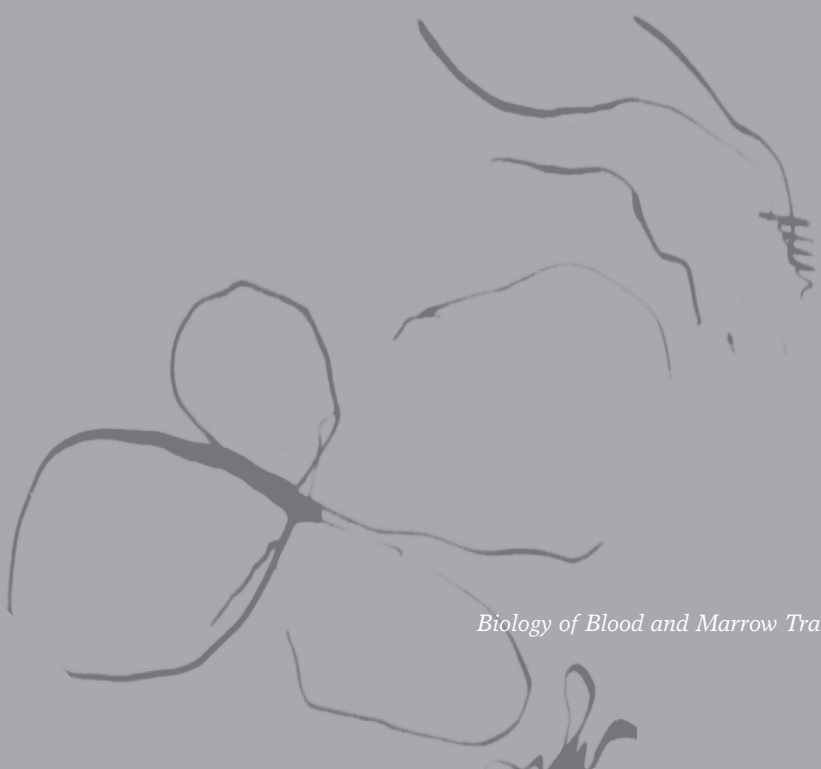
4

Stem cell transplantation nephropathy: a report of six cases

Sabina Kersting and Leo F. Verdonck

Department of Hematology, University Medical Center Utrecht, The Netherlands



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Abstract

Stem cell transplantation (SCT) nephropathy is one cause of chronic kidney disease in patients after allogeneic SCT. It is a thrombotic microangiopathic syndrome characterized by raised creatinine, hypertension, and anemia. The difference with thrombotic thrombocytopenic purpura (TTP)-like syndromes is that it occurs later than 3 months after SCT, has marked renal dysfunction, and occurs in the absence of other complications or nephrotoxic medication. Total body irradiation (TBI) in combination with previous chemotherapy is most likely the cause. We describe 6 cases of SCT nephropathy that occurred in a cohort of 363 patients who received myeloablative allogeneic SCT. All patients had TBI with shielding of the kidneys. We discuss the course of the syndrome, treatment and outcome of the patients.

Introduction

One of the causes of chronic kidney disease after stem cell transplantation (SCT) is a thrombotic microangiopathic condition called bone marrow transplantation nephropathy or SCT nephropathy. The syndrome was first described in 1991, and might occur in up to 20% of patients 1 year after allogeneic SCT. It is characterized by a sudden increase in creatinine, microangiopathic hemolytic anemia, and hypertension occurring typically after 6-12 months. Hereafter, a slower decline in kidney function, leading to end-stage renal disease, but also stabilization can occur.[1-3] Time of onset, presentation and histopathological changes are the same as for radiation nephritis seen previously after radiation for seminomas.

Renal shielding during total body irradiation (TBI) can decrease the chance of developing this syndrome at 2.5 years from around 30% to almost zero.[5] Because this syndrome occurs after a lower dose of irradiation than classical radiation nephritis, other causes might contribute to the pathogenesis.[2] In experimental rat models angiotensine converting enzyme (ACE) inhibitors can treat SCT nephropathy, and treatment with ACE inhibitors is recommended.[6]

Here we describe the clinical course of 6 patients who developed SCT nephropathy in our SCT unit over a period of 11 years and discuss the literature.

Materials and Methods

In this retrospective analysis 6 patients with SCT nephropathy could be traced out of 363 patients who received myeloablative allogeneic SCT from January 1993 to January 2004. SCT nephropathy was defined as the triad of hypertension, disproportionate severe anemia, and sudden rise in serum creatinine with no apparent cause, occuring more than 3 months after SCT.[7]

The charts of the 6 patients were reviewed and hospital course, posttransplant complications and serum creatinines were noted. Patient characteristics and details of the clinical course are shown in Table 1. Creatinine values at different times are shown in Figure 1.

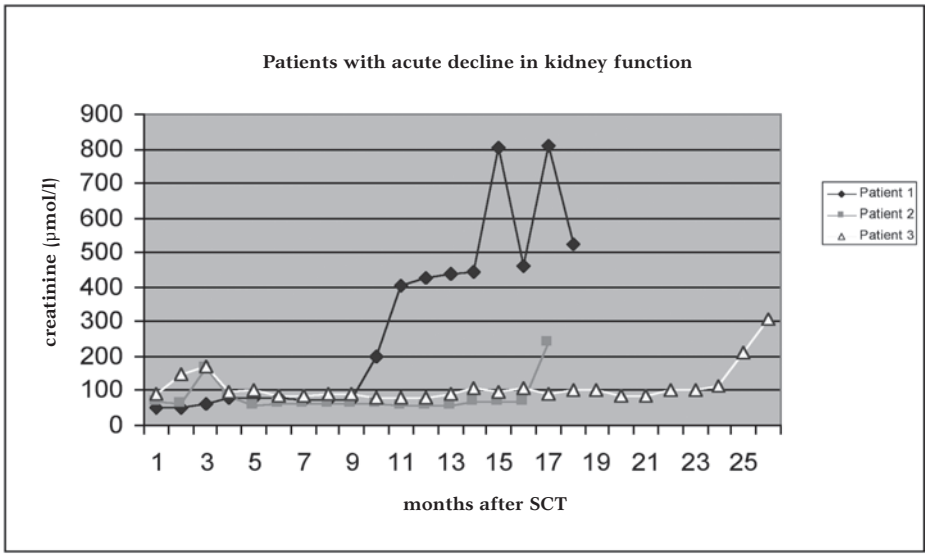
Table 1. Patient characteristics of 6 patients with SCT nephropathy

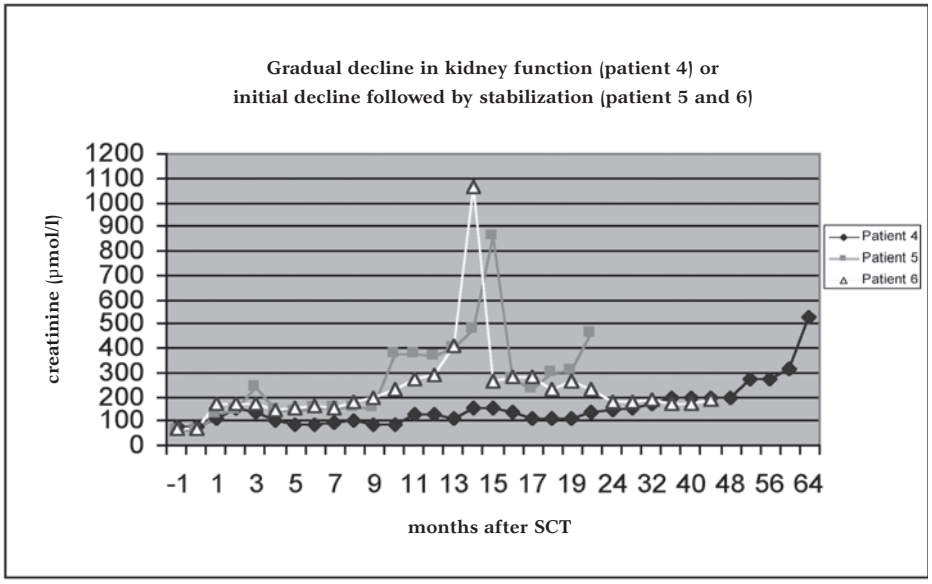
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at SCT	27 years	53 years	25 years	51 years	18 years	51 years
Sex	female	male	female	male	male	female
Disease	AML, first remission	CML, chronic phase	AML, first remission	AML, second remission	ALL, first remission	ALL, first remission
History	no	myocardial infarction	no	diabetes mellitus II	no	hypertension
Previous treatment	cytarabine idarubicine amsacrine	hydrea	cytarabine idarubicine	cytarabine idarubicine amsacrine mitoxantrone etoposide	vincristine asparaginase daunorubicine cytarabine mercaptopurine etoposide cyclophosphamide	vincristine asparaginase daunorubicine cytarabine mitoxantrone
Conditioning	standard*	standard	standard	standard	standard	standard
ATG	no	no	yes	no	no	yes
Transplant	sibling	sibling	MUD	sibling	sibling	MUD
Baseline creatinine	53 µmol/L	61 µmol/L	147 µmol/L	75 µmol/L	56 µmol/L	65 µmol/L
ARF	no	yes	yes	yes	yes	yes
TTP	no	no	yes	no	no	no
aGVHD	no	no	no	no	yes	yes
cGVHD	no	no	no	no	yes	yes
Cyclosporine use	12 weeks	12 weeks	12 weeks	12 weeks	37 weeks	14 weeks
Timing SCTnp	8 months	14 months	32 months	36 months	12 months	13 months
Ultrasonography	normal	normal	normal	loss of parenchyma	decreased right kidney	normal
Kidney biopsy	TMA	not done	not done	not done	TMA	TMA,interstitial nephritis
Proteinuria	0.79 g/L	1.3 g/L	0.90 g/L	1.3 g/L	0 g/L	0.93 g/L
Hematuria	+/-	+	-	+/-	+/-	++
Peak creatinine	987 µmol/L	276 µmol/L	454 µmol/L	869 µmol/L	861 µmol/L	1211 µmol/L
Lowest Hb	4.2 mmol/L	4.2 mmol/L	5.3 mmol/L	4.7 mmol/L	2.3 mmol/L	5.9 mmol/L
Lowest thrombocytes	32 x 10^9/L	19 x 10^9/L	63 x 10^9/L	28 x 10^9/L	125 x 10^9/L	128 x 10^9/L
Highest tension(mmHg)	180/110	220/110	170/120	220/130	170/100	160/105
ACE inhibitor	yes	no	yes	yes	yes	yes
Last kidney function (ml/min/1.73 m^2)	peritoneal dialysis	22	19	peritoneal dialysis	15	29
Time of death and cause	34 months sigmoid perforation	15 months multiorgan failure	alive	alive	20 months pneumonia	alive

Abbreviations: SCT = stem cell transplantation; AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; ALL = acute lymphoblastic leukemia; ATG = antithymocyte globuline; MUD = matched unrelated donor; ARF = acute renal failure defined as doubling of baseline creatinine within 3 months after SCT; TTP = thrombotic thrombocytopenic purpura within 3 months after SCT; aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; SCTnp = stem cell transplantation nephropathy; TMA = thrombotic microangiopathy; GFR = glomerular filtration rate, calculated with MDRD equation: GFR = 186,3 x (serum creatinine)$^{-1.154}$ x age$^{-0.203}$ x (0.742 for women)

* Cyclophosphamide (60 mg/kg/day for 2 days), followed by total body irradiation (600 cGy/day for 2 days) with partial shielding of the lungs (total lung dose 850cGy) and partial shielding of the kidneys (500 cGy/day for 2 days)

Figure 1. Three different courses of SCT nephropathy





Results

Patient 1 was a 27-year-old woman who received SCT because of acute myelogenous leukemia (AML). She was admitted 8 months after SCT because of hypertension, raised creatinine, hemolytic anemia with schistocytes and thrombocytopenia. She received ACE inhibition and a beta-blockade. Her creatinine increased despite adequate treatment of hypertension. Because of uremic pericarditis she started peritoneal dialysis 16 months after SCT. She died of multiorgan failure resulting from perforation of the sigmoid 34 months after SCT.

Patient 2 was a 53-year-old man who received SCT because of chronic myelogenous leukemia (CML). Fourteen months after SCT he was admitted because of abdominal pain, hemolytic anemia with schistocytes, hypertension, thrombocytopenia, raised creatinine and epileptic seizures. Benzodiazepines led to acute respiratory insufficiency and need for mechanical ventilation. Plasma exchange was started to treat suspected thrombotic thrombocytopenic purpura (TTP). Despite this treatment he died of multiorgan failure.

Patient 3 was a 25-year-old woman who received SCT because of AML. Nearly 3 years after SCT she was admitted because of hypertension, raised creatinine, hemolytic anemia with schistocytes, and thrombocytopenia. Her blood pressure normalized with a beta-blockade and ACE inhibition, but creatinine increased slowly. She is now 3 years after SCT and receives treatment for stage 4 chronic kidney disease with a glomerular filtration rate (GFR) of 19 ml/min/1.73 m^2.

Patient 4 was a 51-year-old man who received SCT for AML in second remission. One year after SCT creatinine increased and persistent anemia without an obvious cause developed. Nearly 3 years after SCT hypertension was noted. He was admitted for treatment of hypertension when creatinine was 472 µmol/L 2 years later. ACE inhibition, diuretics and a beta-blockade were started, which led to further rise in creatinine and end-stage renal disease. He started peritoneal dialysis more then 5 years after SCT. Nearly 10 years after SCT he is now in good clinical condition.

Patient 5 was a 18-year-old man who received SCT because of acute lymphoblastic leukemia (ALL). One year after SCT he developed autoimmune hemolytic anemia with hypertension and creatinine of 400 µmol/L. After start with ACE inhibition the creatinine stabilized at 250 µmol/L. The hemolytic anemia did not respond to treatment. He died 20 months after SCT because of pneumonia.

Patient 6 was a 51-year-old woman who received SCT because of ALL. Eight months later beta-blockade was started because of recurrence of hypertension. Five months later ACE inhibition and diuretics were started because of persistence of hypertension, raised creatinine and anemia, and were discontinued shortly hereafter because of worsening of kidney function. After an initial decrease her creatinine rose again

and liver enzyme abnormalities developed. After discontinuation of valacyclovir and treatment with corticosteroids, creatinine decreased. Hypertension was treated with calciumantagonist, and with this treatment kidney function stabilized at GFR of 28 ml/min/1.73 m^2.

Discussion

The diagnosis of individual patients with thrombotic microangiopathy and renal dysfunction after allogeneic SCT can be difficult. Different forms of overlapping thrombotic microangiopathic syndromes have been described. A patient with microangiopathic hemolytic anemia after SCT may therefore be given the diagnosis SCT nephropathy,[1,7-18] radiation nephropathy,[2,19-22] hemolytic uremic syndrome (HUS),[23-28] or TTP.[23,28-30] Pettitt and Clark[26] made a classification of post-SCT thrombotic microangiopathy: 1) multifactorial fulminant thrombotic microangiopathy 2) cyclosporine nephrotoxicity with microangiopathic hemolytic anemia, 3) cyclosporine neurotoxicity with microangiopathic hemolytic anemia, and 4) conditioning-associated HUS. The first 3 syndromes resemble classical TTP and usually develop within 3 months after SCT. The diagnosis of TTP is uncertain following SCT because of the presence of multiple SCT-associated complications[29] and the absence of generally accepted detailed diagnostic criteria.[30] It is even stated that clinical signs of a systemic infection or graft-versus-host disease (GVHD) mimic TTP, and that TTP is not a specific sequla after SCT.[28] Multifactorial thrombotic microangiopathy or TTP on the background of GVHD, infections, or other complications post-SCT has a high mortality.[26] Plasmapheresis or plasma infusion have shown little efficacy in TTP-like conditions following SCT, in contrast to classical TTP.[23,31] Treatment of associated complications is recommended.[28] When patients are receiving cyclosporine, this should be discontinued, but this can lead to deterioration of GVHD. Alternative immunesuppression with corticosteroids should be considered.[26] Cyclosporine nephrotoxicity with microangiopathic hemolytic anemia is a form of TTP that is readily reversible on discontinuation of cyclosporine and treatment of hypertension, and thus has a good prognosis.[26]

Conditioning-associated HUS, the fourth condition mentioned by Petitt and Clark, is almost similar to SCT nephropathy or radiation nephritis, with predominantly raised creatinine levels and hypertension occuring more than 3 months after SCT, with low mortality but frequent residual renal impairment.[26]

The major difference between TTP-like syndromes with renal impairment (multifactorial thrombotic microangiopathy and cyclosporine nephrotoxicity with microangiopathic hemolytic anemia) and SCT nephropathy (radiation nephritis or

conditioning-associated HUS) is the time of occurrence, with TTP usually occuring within 3 months after SCT and SCT nephropathy occurring after 3 months. Other differences are that renal impairment and hypertension are a prerequisite for SCT nephropathy,[7] but can be less dominant in TTP, and that SCT nephropathy occurs in the absence of active complications or toxic medication,[3] whereas TTP often occurs in association with complications like GVHD and infections,[28] or cyclosporine.[32,33]
The hallmark of these syndromes is thrombotic microangiopathy. In SCT recipients, multiple insults may lead to the initiation of endothelial cell injury or dysfunction. These can be conditioning regimens with high-dose chemotherapy or TBI, and increased levels of cytokines in association with acute GVHD (aGVHD) or sinusoidal occlusion syndrome.[32] In addition, cyclosporine may promote procoagulant changes in the endothelium by increasing the release of thromboxane A2 and thromboplastin and increasing ADP, collagen and adrenaline-induced platelet aggregation and factor VII activity and decreasing the production of prostacycline, thrombomodulin and protein C.[30] TBI containing conditioning regimens seem to be the major risk factor for SCT nephropathy.[34]
In our study SCT nephropathy developed in 6 of 363 patients (1.7%). The incidence of SCT nephropathy after allogeneic SCT in adults varies between 0 and 29%, [3,18,19,35,36] with low incidence if the kidneys are shielded.[5] The low incidence of our cohort confirms the efficacy of renal shielding in reducing the incidence of SCT nephropathy.
The first 3 cases show a condition resembling classical TTP, but it is SCT nephropathy because of the time of occurrence, the marked hypertension and increase in serum creatinine. The last 3 cases lack the initial event with thrombocytopenia, but are SCT nephropathy because of the combination of anemia, hypertension and renal impairment in the absence of an obvious cause. In the last 2 patients thrombotic microangiopathy was confirmed by renal biopsies. Previous studies have recognized 3 different courses of SCT nephropathy: acute decline in kidney function (patient 1-3), a more gradual decline in kidney function (patient 4) and an initial decline in kidney function followed by stabilization at a reduced GFR (patient 5 and 6) (Figure 1).[7] SCT nephropathy is a serious condition because it can lead to end-stage renal disease,[8] but acute mortality is lower than in complications-associated TTP-like conditions.[26] In our case-series, 2 patients developed end-stage renal disease, 3 patients developed severe kidney disease stage 4 (GFR 15-29 ml/min/1.73 m^2) and 1 patient died of SCT nephropathy.
ACE inhibition stabilized kidney function in 1 of 5 patients and had no effect in the other 4 patients. These results are not very promising, but because no better treatment is available, ACE inhibition remains the treatment of choice. Plasma

exchange therapy showed not to be effective in the 1 patient who received this treatment, as was described in earlier studies.[30]

Anemia in SCT nephropathy can be caused by thrombotic microangiopathy or erytropoeitin deficiency in a later phase.[1,3] Erytropoeitin deficiency in patients with SCT nephropathy is more pronounced than observed in patients with an equivalent decrease in GFR by another cause.[17] Therefore, erythropoietin is recommended for treatment of anemia in patients with chronic SCT nephropathy.[2] Our 2 patients with end-stage renal disease received this treatment with successful increase in hemoglobin.

Although nephrotoxic drugs (eg cyclosporine and amphotericine B) can cause acute renal failure,[37,38] SCT nephropathy seems not influenced by them.[39] There was no direct relationship in use of nephrotoxic drugs and occurrence of SCT nephropathy in our patients, except for patient 6 who had a combination of thrombotic microangiopathy and interstitial nephritis because of valacyclovir.

Severe proteinuria is not a sign of SCT nephropathy, and was absent in our patients. Nephrotic syndrome in association with chronic GVHD (cGVHD) is an extremely rare complication after myeloablative SCT, but is now more often recognized after nonmyeloablative SCT, even in the absence of cGVHD.[40] Two of our patients had cGVHD, but there was no relationship with development of SCT nephropathy.

In summary, SCT nephropathy is one of the thrombotic microangiopathic syndromes occuring after SCT. It occurs later than TTP-like syndromes, and is characterized by renal dysfunction, anemia, and hypertension, without an obvious cause. It can lead to an acute decline in kidney function or run a more gradual course. Although acute mortality is not so high, it is a serious condition because it can lead to end-stage renal disease. TBI in conditioning regimens is most likely the cause. ACE inhibition is recommended, but certainly cannot prevent deterioration of kidney function in many patients. Treatment with erythropoietin relieves anemia seen later in these patients.

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Chronic kidney disease after myeloablative allogeneic hematopoietic stem cell transplantation

Sabina Kersting[1], Ronald J.Hené[2], Hein A. Koomans[2], Leo F. Verdonck[1]

Departments of [1]Hematology and [2]Nephrology, University Medical Center Utrecht, The Netherlands

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Abstract

Because survival of recipients of allogeneic hematopoietic stem cell transplantation (HSCT) has improved, long-term complications become more important. We studied the incidence and risk factors of chronic kidney disease in these patients and evaluated associated posttransplant complications and mortality.

We performed a retrospective cohort study of 266 adults who received myeloablative allogeneic HSCT and who survived for > 6 months in an 11 year period at a Dutch university medical center. Primary outcome was the incidence of chronic kidney disease defined as a glomerular filtration rate (GFR) of < 60 mL/min/1.73 m^2.

Chronic kidney disease developed in 61 (23%) of 266 patients, with a cumulative incidence rate of 27% at 10 years. Severe kidney disease (GFR of < 30 mL/min/1.73 m^2) developed in 3% of patients. Only 6 patients developed the thrombotic microangiopathic syndrome SCT nephropathy, and 2 of them needed dialysis. Pretransplant risk factors for chronic kidney disease were lower GFR at day 0 ($P < 0.0001$, odds ration [OR] 0.95 95% confidence interval [CI] 0.93-0.97), female sex and higher age ($P = 0.001$ and $P < 0.0001$, respectively). The occurrence of hypertension after HSCT was associated with chronic kidney disease ($P < 0.0001$, OR 0.34 95% CI 0.18-0.62). Mortality was 39% after a mean follow-up of 5.1 years. There was no significant difference in survival between patients with and without chronic kidney disease.

Chronic kidney disease is a common late complication of myeloablative allogeneic HSCT. Because of the natural decline in renal function with time there is a risk of developing end-stage renal disease in the future. SCT nephropathy seems to be a specific cause of chronic kidney disease that is typically associated with severe kidney disease.

Introduction

Chronic kidney disease in the general population is considered to be a public health problem.[1] There is a rising incidence and prevalence of kidney failure.[2] Risk factors include older age, hypertension, diabetes, cardiovascular disease, and a family history of the disease.[1] Detection, evaluation, and management of chronic kidney disease according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines are essential in order to slow progression of chronic kidney disease to kidney failure.[2] More patient groups are now being identified for whom the guidelines are recommended because of an increased risk of developing chronic kidney disease, for example recipients of heart and lung transplantations.[3] It is not well established whether chronic kidney disease is a frequent complication of nonsolid organ transplantation.[4]

Allogeneic hematopoietic stem cell transplantation (HSCT) after intensive chemotherapy and total body irradiation (TBI) (myeloablative conditioning) is a widely accepted approach in the treatment of several hematologic malignancies. Annually approximately 10,000 adults receive an allogeneic HSCT worldwide.[5] Because many recipients of HSCT now have long term survival, late complications, like chronic kidney disease, become more important.[6]

One of the causes of chronic kidney disease after allogeneic HSCT is a microangiopathic syndrome called SCT nephropathy. This syndrome typically occurs 6-12 months following HSCT with the triad hypertension, progressive renal failure and disproportionate severe anemia.[7] However, most cases of chronic kidney disease after HSCT are not accompanied by signs of microangiopathy.[8]

Risk factors described for chronic kidney disease after HSCT are TBI,[9] TBI dose and graft-versus-host disease (GVHD),[10] the absence of renal shielding during TBI,[11] angiotensin-converting enzyme (ACE) gene polymorphism,[12] age, and previous fludarabine administration.[8] Up to now, most of studies analyzing this form of chronic kidney disease have mean follow up of < 3 years,[8-11] or few patients with longer follow-up,[12] and therefore, incidence and causes are not well established.[4]

The aim of this study was to investigate incidence and pretransplant risk factors of chronic kidney disease in recipients of myeloablative allogeneic HSCT with a long follow-up, and to determine posttransplant complications and mortality associated with chronic kidney disease.

Materials and Methods

Study design

Between January 1, 1993 and January 1, 2004 myeloablative allogeneic HSCT was performed in 363 adult patients aged 17-57 years at the Department of Hematology of the University Medical Center Utrecht. Because the primary outcome of this study was chronic kidney disease we excluded patients with a survival of < 6 months (n = 92) and patients with renal dysfunction at baseline (n = 5) (a glomerular filtration rate [GFR] of ≤ 60 ml/min/1.73 m^2 or creatinine ≥ 110 µmol/L). Of these 266 patients data were collected retrospectively using a data base and computerized patient records through February 1, 2006. Patients were treated according to clinical protocols approved by the local investigation review board and gave informed consent.

Study population

All patients received a myeloablative conditioning regimen that consisted of cyclophosphamide (60 mg/kg/day for 2 days), followed by TBI (600 cGy/day for 2 days) with partial shielding of the lungs (total lung dose 850 cGy) and partial shielding of the kidneys (500 cGy/day for 2 days). After the second TBI fraction on day 0, the graft was infused. In recipients of histocompatibility leukocyte antigen (HLA)-matched unrelated donor or a single HLA-antigen mismatched family donor, antithymocyte globulin (Rabbit ATG) (Thymoglobulin™, Sangstat, Amstelveen, the Netherlands) was given before cyclophosphamide was infused. The graft was partial T cell depleted as described earlier.[13]

All patients received GVHD prophylaxis with cyclosporine, which was started on day -2 in a dose of 3 mg/kg/day by continuous infusion for 3-4 weeks, thereafter given orally for 4-6 weeks in a dose that gave comparable trough levels. Dose adjustments were made to keep cyclosporine trough levels between 200 and 450 ng/mL. When no active GVHD disease was present, cyclosporine was discontinued within 3 months after HSCT. GVHD was diagnosed according to the Seattle criteria.[14] Acute GVHD (aGVHD) grade I was treated with topical corticosteroids. aGVHD grade II or higher was treated with high-dose systemic corticosteroids. Limited chronic GVHD (cGVHD) was not treated and extensive cGVHD was treated with systemic corticosteroids.

Infection prophylaxis consisted of ciprofloxacin, fluconazole and amphotericine B given orally until granulocyte counts exceeded 500 cell/µl. Cephalotin was given intravenously from day +3 until day +13. Co-trimoxazol 480 mg twice daily and valacyclovir 500 mg twice daily were given orally from day +1 until 12 months after HSCT or longer in case of active GVHD.

Data collection

The following data on pretransplant risk factors were collected: history of hypertension, previous autologous transplantation, sex, age, type of transplant, mismatched transplant, underlying disease, presence of high risk malignancy and estimated GFR on day 0. For each patient serum creatinine was collected at day 0, 6 months after HSCT, 12 months after HSCT and thereafter annually.

The following complications were recorded: 1) acute renal failure, 2) aGVHD, cGVHD and the duration of cyclosporine use in patients with aGVHD, cGVHD, 3) thrombotic thrombocytopenic purpura (TTP), 4) Sinusoidal occlusion syndrome 5) cytomegalovirus (CMV) reactivation, 6) hypertension, and 7) the occurrence of SCT nephropathy. Mortality data were collected.

Definitions

Patients with acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase and untreated severe aplastic anemia were considered low risk; all other hematologic diseases were considered high risk.

Acute renal failure was defined as doubling of baseline serum creatinine within 3 months after HSCT. TTP was defined as simultaneous occurrence of thrombocytopenia and hemolytic anemia with red cell fragmentation, raised lactate dehydrogenase, raised bilirubin and decreased haptoglobin level, if this occurred within 3 months after HSCT. Sinusoidal occlusion syndrome was defined as hyperbilirubinemia, right upper quadrant pain, and weight gain occurring within 20 days post-transplantation. Hypertension was defined as a systolic pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher or receiving medication for treatment of hypertension.

Chronic kidney disease was defined according to the K/DOQI definition of kidney disease.[2] Stage 3 chronic kidney disease was an estimated GFR < 60 mL/min/1.73 m^2, stage 4 chronic kidney disease was a GFR < 30 mL/min/1.73 m^2 and stage 5 chronic kidney disease a GFR < 15 mL/min/1.73 m^2 or need for dialysis.[2,8] Only if low GFR developed after at least 6 months after HSCT and persisted until death or last follow-up, the patient was defined as having chronic kidney disease. Estimated GFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation, defined as GFR = 186,3 x (serum creatinine)$^{-1.154}$ x age$^{-0.203}$ x (0.742 for women).[15] SCT nephropathy was defined as the triad of hypertension, hemoglobin of ≤ 6.0 mmol/L and rise in serum creatinine to > 250 µmol/L, with no apparent cause occurring > 3 months after HSCT.

Statistical analysis

Continuous variables are displayed as mean, with ranges in parentheses. For dichotomous variables the frequency of occurrence is given along with the corresponding percentage. Cumulative incidence rates were made for chronic kidney disease.

Differences between groups were assessed with the chi-square test or Fisher's exact test (where appropriate). A two-sided Student's t-test was used for continuous variables.

The relative contributions of continuous and dichotomous variables on the outcome chronic kidney disease were examined using stepwise multiple logistic regressions. Survival was analyzed by the Kaplan-Meier method. All P-values were two-sided, and a value of < 0.05 was considered statistically significant. All analysis was performed using SPSS version 12.0 (SPSS Inc, Chicago IL, USA).

Competing risk data were used to make a cumulative incidence for chronic kidney disease, with outcome being chronic kidney disease, competing risk being death without chronic kidney disease, and time variable being time to chronic kidney disease, death or last follow-up, whichever was first. This analysis was performed using an R-library for multistate models and SPSS version 14.0.[16]

Results

Table 1 shows the pretransplant risk factors of the 266 recipients of myeloablative allogeneic HSCT. The mean follow-up time was 5.1 years (range 0.5-13.1 years). The mean age at day 0 was 38.3 years (range 17-56 years). Chronic kidney disease developed in 61 out of 266 patients (23%) after a mean of 2.6 years (range 0.5-12 years). Eight of these patients had severe chronic kidney disease stage 4 and 5, with a GFR < 30 mL/min/1.73 m^2 after a mean of 3.3 years (range 1.7-5.4 years) in 6 of them and need for dialysis after a mean of 6.3 years (2.8 and 9.8 years, respectively) in 2 of them. The cumulative incidence rates for chronic kidney disease were 20% at 5 years and 27% at 10 years (Figure 1).

The renal function slowly deteriorated in time (Figure 2).

Renal-vascular complications that developed were as follows: Acute renal failure in 118 patients (44%), TTP in 4 patients (1.5%), hypertension in 46 patients (17%) and SCT nephropathy in 6 patients (2%) (Table 2). SCT nephropathy was the cause of stage 4 chronic kidney disease in 2 of 6 patients (33%) and the only cause of need for dialysis.

Table 1. Pretransplant risk factors of patients with and without CKD

	Patients with CKD	Patients without CKD	P-value	Multivariate OR (95% CI)
Number of patients	61 (23%)	205 (77%)		
Sex			0.001	
Male	25 (41%)	136 (66%)		
Female	36 (59%)	72 (34%)		
Age mean (range)	43.2 (18-55)	36.8 (17-56)	< 0.0001	
> 40 years	19 (31%)	112 (55%)		
< 40 years	42 (69%)	93 (45%)		
History			ns	
No history	53 (85%)	175 (85%)		
Hypertension	7 (12%)	17 (8%)		
Autologous transplantation	2 (3%)	13 (6%)		
Transplant			ns	
Related donor	49 (80%)	150 (73%)		
Matched unrelated donor	12 (20%)	55 (27%)		
Mismatch			ns	
Yes	4 (7%)	20 (10%)		
No	57 (93%)	185 (90%)		
Disease			ns	
AML	13 (21%)	55 (27%)		
ALL	6 (10%)	37 (18%)		
CML	15 (25%)	46 (22%)		
SAA	1 (2%)	9 (4%)		
MM	12 (20%)	23 (11%)		
Other	14 (23%)	35 (17%)		
High risk			ns	
Yes	39 (64%)	118 (58%)		
No	23 (36%)	87 (42%)		
Baseline sCr (µmol/L) mean (range)	68.4 (50-104)	64.4 (37-108)	0.026	
Baseline GFR (ml/min/1.73 m^2) mean (range)	102.5 (61-176)	122.9 (63-206)	< 0.0001	0.95 (0.93-0.97)

Abbreviations: CKD = chronic kidney disease; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia; SAA = severe aplastic anemia; MM = multiple myeloma; sCr = serum creatinine; GFR = glomerular filtration rate

Figure 1. Cumulative incidence of CKD and survival

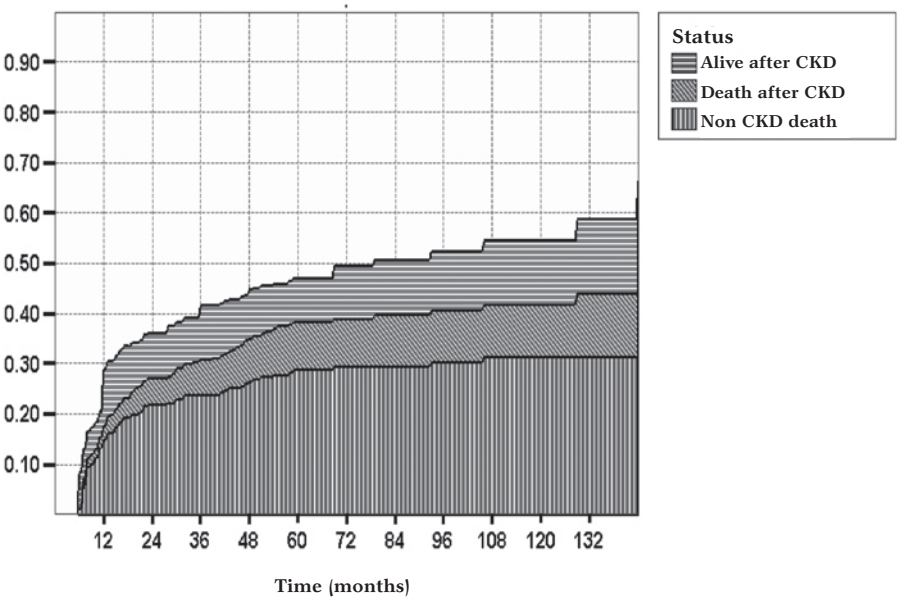

Figure 2. Evolution of kidney function of all patients with CKD

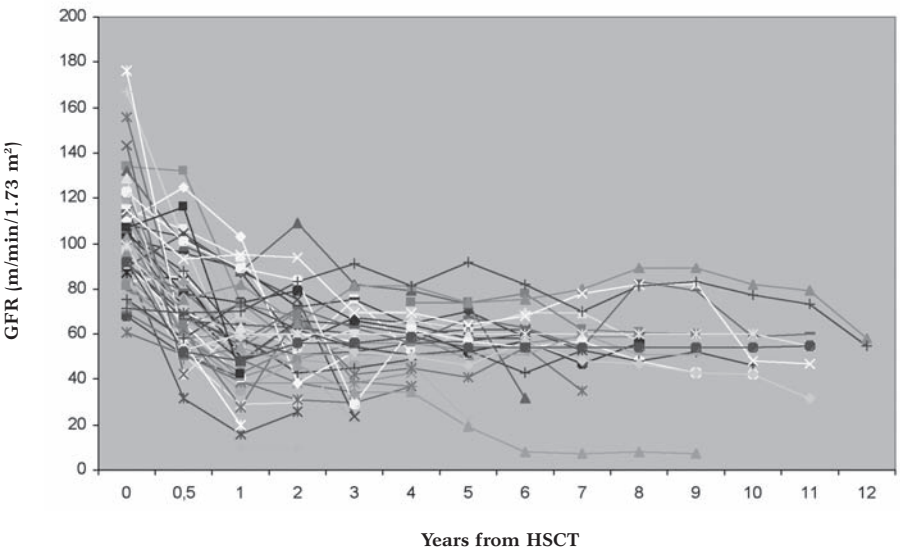

Table 2. Posttransplant complications, treatment, and mortality of patients with and without CKD

	Patients with CKD	Patients without CKD	P-value	Multivariate OR (95% CI)
Number of patients	61 (23%)	205 (77%)		
ARF			ns	
Yes	28 (46%)	90 (44%)		
No	33 (54%)	115 (56%)		
SOS			ns	
Yes	1 (2%)	4 (2%)		
No	60 (98%)	201 (98%)		
TTP			ns	
Yes	1 (2%)	3 (2%)		
No	60 (98%)	202 (99%)		
CMV reactivation			ns	
Yes	11 (18%)	31 (15%)		
No	50 (82%)	174 (85%)		
aGVHD			ns	
No-grade I	33 (54%)	125 (61%)		
II-IV	28 (46%)	80 (39%)		
cGVHD			ns	
No	34 (56%)	129 (63%)		
Limited	14 (23%)	44 (22%)		
Extensive	13 (21%)	32 (16%)		
Hypertension			< 0.0001	0.34 (0.18-0.62)
Yes	22 (36%)	24 (12%)		
No	35 (57%)	165 (81%)		
Missing	4 (7%)	16 (8%)		
SCT nephropathy				
Yes	5 (8%)	1 (1%) *		
No	56 (92%)	204 (99%)		
Cyclosporine use in weeks mean (range)	15.5 (4-80)	19.3 (5-220)	ns	
Hemoglobin (mmol/L) mean (range)	7.37 (5.0-8.9)	7.74 (5.1-9.7)	0.004	
Mortality			ns	
Alive	35 (57%)	127 (62%)		
Dead	26 (43%)	78 (38%)		

Abbreviations: CKD = chronic kidney disease; ARF = acute renal failure; SOS = sinusoidal occlusion syndrome; TTP = thrombotic thrombocytopenic purpura; CMV = cytomegalovirus; aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; SCT = stem cell transplantation

*died before developing chronic renal failure

Univariate analysis of pretransplant risk factors revealed that patients who developed chronic kidney disease were more often women (P = 0.001), were older (P < 0.0001), had lower GFR (P < 0.0001) and higher serum creatinine (P = 0.026) (Table 1). In multivariate analysis only lower estimated GFR (P < 0.0001, odds ration [OR] 0.952 95% confidence interval [CI] 0.933-0.972) was a pretransplant risk factor for chronic kidney disease. Diagnosis, type of transplant, mismatched transplant, presence of high risk malignancy, history of hypertension and previous autologous HSCT did not differ statistically between the groups with or without chronic kidney disease.
In univariate and multivariate analysis of posttransplant complications only the occurrence of hypertension after HSCT was associated with chronic kidney disease (P < 0.0001 and P < 0.0001, OR 0.337 95% CI 0.184-0.617). Acute renal failure, TTP, sinusoidal occlusion syndrome, aGVHD, cGVHD, CMV reactivation and longer cyclosporine use did not differ statistically between the groups with or without chronic kidney disease.
At day 0, 233 patients (88%) had a GFR $\geq$ 90 mL/min/1.73 m^2, and 45 of them (19.3%) developed chronic kidney disease, 33 patients had a GFR between 61 and 89 mL/min/1.73 m^2, and 16 of them (51.5%) developed chronic kidney disease.
Of the patients who developed hypertension after HSCT, there was no significant difference in the use of antihypertensive medication between the patients with or without chronic kidney disease.
Mean hemoglobin was significantly lower in patients with chronic kidney disease compared to patients without chronic kidney disease (P = 0.004).
Mean follow-up of surviving patients was 7.0 years (range 1.7-13.1 years). Death occurred in 107 patients (39%) after a mean of 2.1 years (range 0.5-12.6 years) because of relapse (18%) or treatment related mortality (TRM) (21%). There was no significant difference in survival between patients with and without chronic kidney disease (P = 0.98).

Discussion

In this large study with long follow-up after myeloablative allogeneic HSCT chronic kidney disease developed in 62 of 271 patients (23%) after mean follow-up of 5.1 years. This is more than twice as high as seen in a community-based population with a mean age of 43, where 9.4% developed chronic kidney disease after mean follow up of 18.5 years.[17] In most of our patients chronic kidney disease was unnoticed by their doctors. We found that although chronic kidney disease developed in the first year in the majority of patients it even developed in patients after 12 years of

follow-up. The study that used the same methods to determine kidney disease had an incidence of 12% at 2 years.[8]

It is known that chronic kidney disease is a risk factor for cardiovascular disease.[18] Decreased GFR is associated with complications in almost all organ systems. Among the most important complication are high blood pressure, anemia, malnutrition, bone disease, neuropathy and decreased overall functioning and well being.[2] This was shown in our patient cohort by lower mean hemoglobin in the group with chronic kidney disease.

The strongest pretransplant risk factor for the development of chronic kidney disease was lower estimated GFR at day 0. Also, in community-based population studies lower GFR was a predictor for the development of kidney disease.[17] Therefore, it is likely that patients with suboptimal kidney function before HSCT will have more chance of developing chronic kidney disease after HSCT. Patients with a GFR between 61 and 89 mL/min/1.73 m^2 before HSCT had > 50% chance of developing chronic kidney disease in this study.

Other pretransplant risk factors for chronic kidney disease in univariate analysis were age and female sex. Age as a risk factor for chronic renal failure was also found in another study of patients after HSCT.[8] Cross-sectional community studies showed progressive decline in renal function with aging.[19] Renal aging is a natural phenomenon with a course that is dependent on a combination of genetic and environmental factors. Pathophysiological mechanisms involved are the renin-angiotensin system activity, reduced renal klotho gene expression, increased oxidative stress, and genes involved in cellular cycle regulation.[20] The association of female sex with chronic kidney disease is not a new finding. In other studies the cutoff value of an estimated GFR of < 60 mL/min/1.73 m^2 for women was lowered because of a 50% more incidence of chronic kidney disease in women with this cutoff value using the MDRD equation.[17]

Hypertension after HSCT in our cohort was associated with chronic kidney disease. Hypertension is known to be both a cause and a complication of chronic kidney disease. Hypertension in patients with chronic kidney disease is associated with faster loss of kidney function and development of cardiovascular disease.[2] Furthermore, low target blood pressure of 130/80 mmHg delays the onset of kidney failure,[21] and, therefore, treatment of hypertension to a target of less than 130/80 in patients with chronic kidney disease is recommended.[22] The use of antihypertensive medication in our cohort did not differ statistically between hypertension patients with or without chronic kidney disease, suggesting that treatment could not prevent the development of chronic kidney disease. However, whether the above mentioned targets were met is not known.

Acute renal failure was not associated with chronic kidney disease. Major risk factors for acute renal failure are sinusoidal occlusion syndrome,[23] TTP,[24] aGVHD,[25,27] and nephrotoxic medication like cyclosporine[28] and amphothericine B.[26] Because acute renal failure was not associated with chronic kidney disease, it is unlikely that short term use of nephrotoxic medication have caused chronic kidney disease in this cohort. Longer duration of cyclosporine treatment was not associated with chronic kidney disease.

SCT nephropathy was associated with severe chronic kidney disease. It was the cause of stage 4 chronic kidney disease in 33% of patients and the only cause for end-stage renal failure. This microangiopathic syndrome characterized by hypertension, progressive renal failure and disproportionate severe anemia resembles radiation nephritis described > 50 years ago as a complication of radiotherapy for seminomas.[29] The role of TBI in the development of SCT nephropathy seems clear from previous studies.[7-12] Treatment with ACE inhibitors have shown efficacy in prevention and treatment of SCT nephropathy in experimental rat models. Treatment with ACE inhibitors is recommended for patients with this complication.[30]

Survival was not influenced by chronic kidney disease in this cohort. The reason for this might be that follow-up was still too short for development of late complications of chronic kidney disease.

A limitation of our study is that the mechanisms underlying chronic kidney disease after HSCT are not clear. Only 6 patients with chronic kidney disease had the microangiopathic syndrome SCT nephropathy. Whether thrombotic microangiopathy also play a role in the development of chronic kidney disease in patients without SCT nephropathy is not clear.

Because all patients had the same conditioning regimen, and had the same immunesuppression and infection prophylaxis, it was not possible to asses the risk of these components for chronic kidney disease. Therefore, it remains unknown whether chronic kidney disease is associated with TBI or with the total conditioning regimen, or whether it is a side effect of standard immunesuppression and antibiotics used after HSCT.

In conclusion, chronic kidney disease is a common late complication after HSCT developing in 23% of patients, with a cumulative incidence of 27% at 10 years post-transplantation. Severe kidney disease develops in 3% of patients. Chronic kidney disease can develop between a half year to 12 years or even later. Because of the natural decline in renal function with time there is a risk of developing end-stage renal disease in the future. Pretransplant risk factors for chronic kidney disease are lower GFR at day 0, higher age and female sex. The occurrence of hypertension after HSCT is associated with chronic kidney disease. SCT nephropathy seems to be a specific cause that is typically associated with severe kidney disease.

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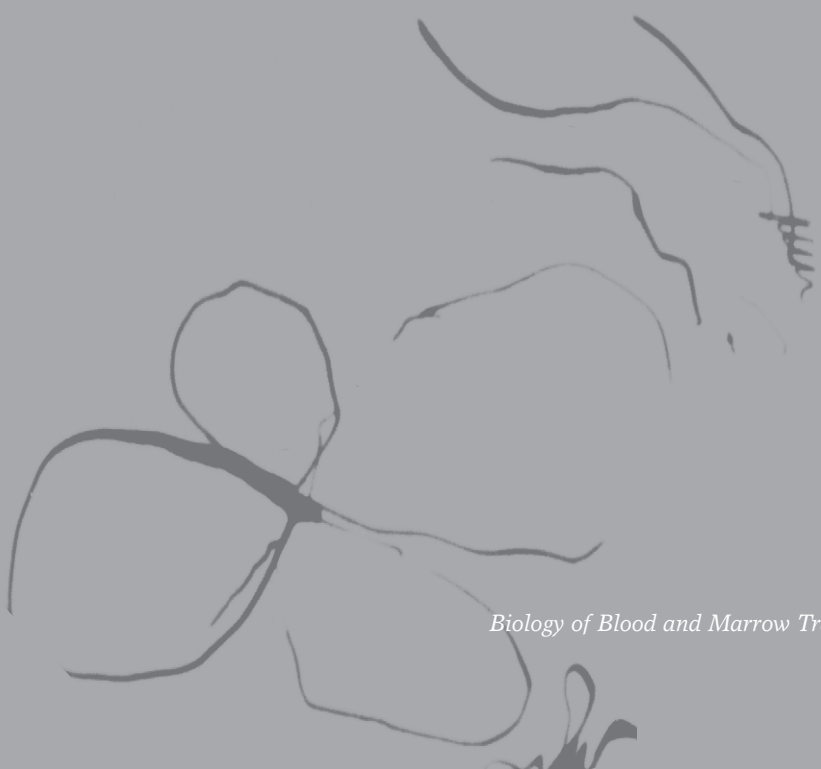
Chronic kidney disease after nonmyeloablative stem cell transplantation in adults

Sabina Kersting and Leo F. Verdonck

Department of Hematology, University Medical Center Utrecht, The Netherlands



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Abstract

Chronic kidney disease (CKD) after myeloablative stem cell transplantation (SCT) is a well established problem. Little is known about CKD after nonmyeloablative SCT. We performed a retrospective cohort study of 108 adults who received nonmyeloablative SCT with fludarabine and/or total body irradiation (TBI) conditioning. Renal function was assessed by estimating glomerular filtration rate (GFR) with the MDRD equation. CKD was defined as GFR < 60 mL/min/1.73 m^2.

CKD developed in 15% of patients after a median of 15 months. None of the patients required dialysis. Cumulative incidence of CKD was 7% at 12 months, 14% at 24 months and 22 % at 48 months. Risk factors for CKD were female sex ($P = 0.021$), older age ($P = 0.040$) and lower GFR pretransplant ($P < 0.001$). Complications after SCT were not associated with CKD. SCT nephropathy, a cause of CKD after myeloablative SCT, did not occur. Overall survival (OS) was 66%. There was no difference in survival between patients with or without CKD.

CKD is a frequent complication after nonmyeloablative SCT and is not related to SCT nephropathy. Women, patients above 50 years of age and patients with slightly decreased kidney function pretransplant have the greatest risk of development of CKD.

Introduction

Because treatment-related morbidity and mortality (TRM) limit the success of myeloablative stem cell transplantation (SCT), a nonmyeloablative SCT regimen was developed. This regimen would be suitable for patients of older age and also for patients with comorbid conditions who were not eligible for myeloablative SCT.[1] Differences between myeloablative and nonmyeloablative conditioning are a reduction in intensities of both chemotherapy and total body irradiation (TBI) in the nonmyeloablative approach. Because patients' characteristics and transplant procedures are different in the two regimens, it is likely that transplant-related organ dysfunction after SCT will be different also.

Chronic kidney disease (CKD) after myeloablative SCT is a well established problem. Incidence of CKD after myeloablative SCT ranges between 7% and 66%, dependent on different definitions that were used.[2-9] Two recent large studies showed an incidence of CKD (defined according to Kidney Disease Outcomes Quality Initiative [K/DOQI] as an estimated glomerular filtration rate [GFR] of < 60 ml/min/1.73 m^2 for more than 3 months)[10] after myeloablative SCT of 22.3% and 23%, respectively.[11,12] Detection of patients with CKD is important, because these patients have adverse outcomes, such as kidney failure, cardiovascular disease, and premature death, which can be prevented or delayed by interventions.[10] A subset of patients with CKD after myeloablative SCT has a thrombotic microangiopathic syndrome known as SCT nephropathy, radiation nephritis or conditioning-associated HUS, wherein TBI is the most probable cause.[13-24] These patients have a higher risk for development of end-stage renal disease with increased mortality.[3,12] Because TBI dose is lower in nonmyeloablative SCT, the development of CKD might be less. However, patients receiving nonmyeloablative transplants are usually older, and renal function declines with age,[25] which may increase the incidence of CKD after nonmyeloablative SCT.

Until now only 1 study describes chronic renal dysfunction after nonmyeloablative SCT, with an incidence of 66% defined by reduction of GFR of at least 25% from baseline.[26] How many of these patients have a GFR < 60 ml/min/1.73 m^2 (K/DOQI definition of CKD) is not clear from this study. This particular cutoff is important because of the increased prevalence of hypertension, anemia, derangements in calcium-phosphorous metabolism, reduction in serum albumin, and reductions in functional status that occur below this cutoff.[10]

The aim of the present study was to evaluate the prevalence of CKD (defined as a GFR < 60ml/min/1.73 m^2) and to analyze risk factors for CKD in a large cohort. Moreover, we wanted to study whether CKD influenced survival.

Patients and Methods

Patients

Between September 1, 2001 and October 1, 2005, nonmyeloablative SCT was performed in 150 adults aged 20-69 years, at the Department of Hematology of the University Medical Center Utrecht. Because the primary outcome of this study was CKD, we excluded patients with a survival of < 6 months (n = 24) or with a GFR ≤ 60 ml/min/1.73 m^2 (n = 18) within 1 month prior to SCT. Patients gave informed consent and were treated according to clinical protocols approved by the local ethics review board.

Methods

Of the 108 remaining patients, data were collected and analyzed retrospectively using a database and patient records through December 1, 2006. The following baseline variables were noted: sex, age, history of autologous transplantation, history of hypertension (defined as a blood pressure ≥ 140/80 mmHg or receiving anti-hypertensive medication), history of vascular disease (angina pectoris, myocardial infarction, cerebrovascular event and diabetes mellitus), diagnosis of hematologic disease, malignancy risk (low risk malignancy: patients with acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase and untreated severe aplastic anemia [SAA]; high risk malignancy: all other hematologic diseases), type of transplant (matched related donor, partially matched related donor, matched unrelated donor), and conditioning regimen.

Serum creatinine was noted at 6 months, 8 months, 12 months, 18 months and 24 months and thereafter annually. Renal function was assessed by estimating GFR with the simplified Modification of Diet in Renal Disease Study prediction equation: GFR = 186,3 x (serum creatinine)$^{-1.154}$ x age$^{-0.203}$ x (0.742 for women).[10] CKD was defined according to the K/DOQI definition of kidney disease. Stage 3 CKD was an estimated GFR < 60 mL/min/1.73 m^2, stage 4 CKD was a GFR < 30 mL/min/1.73 m^2 and stage 5 CKD a GFR < 15 mL/min/1.73 m^2 or need for dialysis.[10] Only if low GFR persisted until death or last follow-up, the patient was defined as having CKD.

Acute renal failure was defined as occurrence of renal dysfunction within 100 days after SCT. Acute renal failure was categorized as follows: grade 0 (or normal renal function) was equivalent to a decrease in estimated GFR of < 25% of the value at time of SCT. Grade 1 corresponded to < two-fold rise in serum creatinine concentration, with a decrease in estimated GFR of > 25% of the value at time of SCT. Grade 2 corresponded to > two-fold rise in serum creatinine, without indication for dialysis.

Grade 3 corresponded to patients with grade 2 parameters but requiring dialysis. This classification of grades of acute renal failure is similar to other studies on acute renal failure after SCT.[26-28]

Nephrotic syndrome was defined as a urinary protein excretion > 3.5 g/24 hr and hypoalbuminemia with plasma levels < 3g/dl.

The following variables posttransplantation were registered until last follow-up or death: acute and chronic graft-versus-host disease (aGVHD, cGVHD), cytomegalovirus (CMV) reactivation, admission to intensive care unit (ICU), hypertension and cyclosporine trough levels.

SCT procedure

The nonmyeloablative conditioning regimen consisted of fludarabine (30 mg/m^2/day for 3 days) followed by TBI of 200 cGy (n = 76) or TBI alone (n = 32). The graft was infused after TBI on day 0. In recipients of a histocompatibility leukocyte antigen (HLA)-matched unrelated donor or a single HLA-antigen mismatched family donor, antithymocyte globulin (Rabbit ATG, Thymoglobulin™,Genzyme, Cambridge. MA) was given before fludarabine was infused, at a dose of 2 mg/kg/day for 4 days (n = 41).

All patients received GVHD prophylaxis orally with cyclosporine and mycophenolate mofetil (MMF). Cyclosporine was started on day -3 at 4,5 mg/kg twice daily and continued until day +84 (n = 66) or +120 (n = 42), followed by tapering if no GVHD was present. Dose adjustments were made to keep cyclosporine trough levels between 200 ng/mL and 400 ng/mL. Moreover, cyclosporine dose was lowered when creatinine rise was caused by cyclosporine, at the discretion of the physician. MMF was started 5 hours after graft infusion at 45 mg/kg/day with a maximum dose of 3 g/day until day +28 (n = 66) or +84 (n = 42), followed by tapering if no GVHD was present. GVHD was diagnosed according to the Seattle criteria.[29] aGVHD grade I was treated with topical corticosteroids. aGVHD grade II or higher was treated with high-dose systemic corticosteroids. Limited cGVHD was not treated and extensive cGVHD was treated with cyclosporine, systemic or topical corticosteroids, MMF or a combination of these drugs.

Infection prevention consisted of ciprofloxacin and fluconazole, given orally, until granulocyte counts exceeded 500 cell/µl. Co-trimoxazol 480 mg twice daily was given for 15 months and valacyclovir 500 mg twice daily was given for 12 months, both orally.

Statistical analysis

Continuous variables are displayed as the median, with range in parentheses. For dichotomous variables, the frequency of occurrence is given along with the corresponding percentage. For comparison of characteristics between groups, a chi-square test was used to compare proportions, and two-sided Student's t-test to compare continuous outcomes. Those parameters reaching univariable significance level of $P \leq 0.1$ were assessed for significance using multiple logistic regressions.

Kaplan-Meier survival curves were made for overall survival (OS). Curves were compared with log-rank test. All P-values were two-sided and a value of < 0.05 was considered statistically significant. Analysis was performed using SPSS version 12.0 (SPSS Inc, Chicago II, USA).

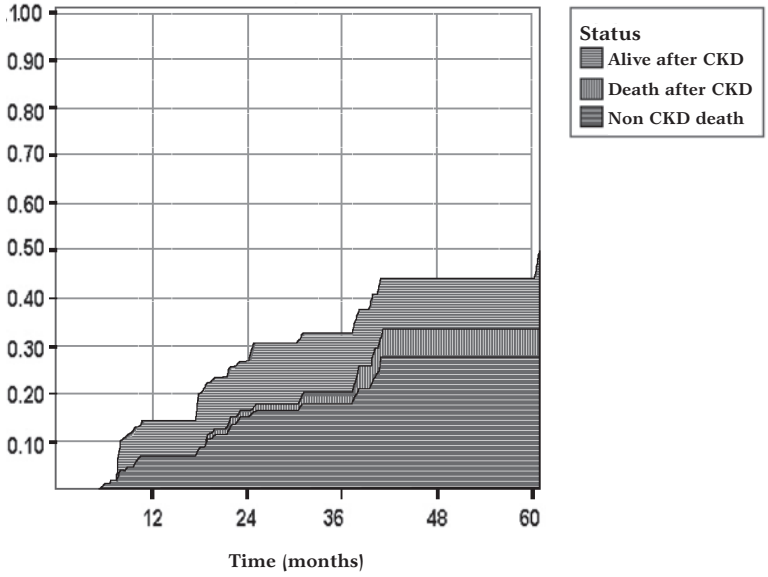
Competing risk data were used to make a cumulative incidence for CKD, wherein outcome is CKD, competing risk is death without CKD, and time variable is time to CKD, death or last follow-up, whichever was first. This analysis was performed using an R-library for multistate models and SPSS version 15.0.[30]

Results

CKD stage 3 (GFR < 60 mL/min/1.73 m^2) developed in 14 patients (13%) and CKD stage 4 (GFR < 30 mL/min/1.73 m^2) developed in 2 patients (2%) after a median of 15 months (range 1-48 months). None of the patients required dialysis. Median follow-up for surviving patients was 29 months (range 15-61). Cumulative incidence of CKD was 7 % at 12 months, 14 % at 24 months, 16% at 36 months and 22% at 48 months (Figure 1). OS was 66% at 48 months. There was no difference in survival between patients with and without CKD.

Pretransplant risk factors for CKD stage 3 and 4 were female sex ($P = 0.021$), older age ($P = 0.040$) and lower GFR 1 month prior to SCT ($P < 0.001$) (Table 1). Patients older than 60 years (n = 30), patients between 50 and 59 years (n = 48), and patients between 40 and 49 years (n = 20) developed CKD in 17%, 21% and 5% respectively. None of the patients younger than 40 years (n = 10) developed CKD. Patients with GFR < 90 ml/min/1.73 m^2 (n = 47) progressed to CKD in 23% of cases, patients with GFR between 90 and 120 ml/min/1.73 m^2 (n = 43) progressed to CKD in 12% of cases. None of the patients with GFR > 120ml/min/1.73 m^2 developed CKD. In multivariate analysis only lower GFR 1 month prior to SCT was associated with CKD stage 3 and 4 ($P = 0.027$, odds ratio 0.96, 95% confidence interval 0.924-0.995). Diagnosis, high risk malignancy, type of transplant, conditioning regimen, and a history of hypertension, autologous transplantation or vascular disease did not differ between patients with or without CKD stage 3 and 4.

Figure 1. Cumulative incidence and survival of patients with and without CKD



None of the complications after SCT was associated with CKD (Table 1). Moreover, immunesuppression regimen (cyclosporine until day +84 and MMF until day +28 or cyclosporine until day +120 and MMF until day +84), cyclosporine trough levels, or long-term cyclosporine use in case of cGVHD did not differ between the groups with or without CKD. Three patients developed nephrotic syndrome, but none of them developed CKD. No patient developed thrombotic thrombocytopenic purpura, sinusoidal occlusion syndrome or SCT nephropathy. Patients who developed CKD had significantly lower hemoglobin (Hb) at 12 months than patients who did not (Hb 8.0 mmol/L, range 5.0-10.4 versus Hb 8.6 mmol/L, range 5.8-10.5, P = 0.036).

Discussion

In this large single-center cohort of recipients of nonmyeloablative SCT, 15% of patients developed CKD after a median follow-up of 29 months. This is higher compared to the general population of the same age, where CKD is present in < 10%.[31] The cumulative incidence of CKD was 22% at 48 months, which is slightly higher than a cumulative incidence of CKD of 20% at 5 years seen after myeloablative SCT at the same institution.[12] The most likely rationale for this is that

Table 1. Risk factors and outcome of patients with and without CKD

	All patients	CKD grade 3-4	no CKD	P-value	Multivariate OR (95% CI)
Sex				0.021	
Male	70 (64.8%)	6 (37.5%)	64 (69.6%)		
Female	38 (35.2%)	10 (62.5%)	28 (30.4%)		
Age	55 (20-66)	55.5 (44-65)	55 (20-66)	0.04	
History					
Autologous	46 (42.6%)	8 (50.0%)	38 (41.3%)	ns	
Hypertension (>140/90 mmHg)	43 (39.8%)	10 (62.5%)	33 (35.9%)	ns	
Vascular disease	10 (9.3%)	2 (12.5%)	8 (8.7%)		
Diagnosis				ns	
Acute myelogenous leukemia	17 (15.7%)	0 (0%)	17 (18.5%)		
Acute lymphoblastic leukemia	4 (2.7%)	1 (6.3%)	3 (3.3%)		
Chronic myelogenous leukemia	4 (2.7%)	1 (6.3%)	3 (3.3%)		
Severe aplastic anemia	4 (3.7%)	0 (0%)	4 (4.3%)		
Multiple myeloma	48 (44.4%)	9 (56.3%)	39 (42.4%)		
Other	31 (28.7%)	5 (31.3%)	26 (28.3%)		
Malignancy Risk				ns	
High risk	87 (80.6%)	14 (87.5%)	73 (79.3%)		
Low risk	21 (19.4%)	2 (12.5%)	19 (20.7%)		
Type of transplant				ns	
Matched related donor	70 (64.8%)	8 (50.0%)	62 (67.4%)		
Partially matched related donor	7 (6.5%)	2 (12.5%)	5 (5.4%)		
Matched unrelated donor	31 (28.7%)	6 (37.5%)	25 (27.2%)		
Mismatch	15 (13.9%)	4 (25.0%)	11 (12.0%)		
Conditioning				ns	
Fludarabine/TBI	35 (32.4%)	2 (12.5%)	33 (35.9%)		
Fludarabine/TBI/ATG	41 (38.0%)	8 (50.0%)	33 (35.9%)		
TBI	32 (29.6%)	6 (37.5%)	26 (28.3%)		
Renal function					
Estimated GFR -1 month	94 (62-156)	81.5 (62-102)	99 (63-156)	P<0.001	0.96 (0.924-0.995)
Estimated GFR baseline	87 (61-187)	76 (66-120)	88.5 (61-187)	ns	
Creatinine -1 month	73 (48-129)	77 (58-112)	72.5 (48-129)	ns	
Creatinine baseline	77 (47-112)	77 (57-101)	77 (47-112)	ns	
Immune suppression				ns	
Cyclosporine +84 days	66 (61.1%)	9 (56.3%)	57 (62.0%)		
Cyclosporine +120 days	42 (38.9%)	7 (43.8%)	35 (38.0%)		
Complications					
Acute renal failure	32 (29.6%)	6 (37.5%)	26 (28.3%)	ns	
Nephrotic syndrome	3 (2.8%)	0 (0%)	3 (3.3%)	ns	
Hypertension within 100 days	30 (27.8%)	5 (31.3%)	25 (27.2%)	ns	
Chronic hypertension	30 (27.8%)	5 (31.3%)	25 (27.2%)	ns	
CMV reactivation	11 (10.2%)	2 (12.5%)	9 (9.8%)	ns	
ICU admission	5 (4.6%)	1 (6.3%)	4 (4.3%)	ns	
Acute GVHD grade 0-I	63 (58.3%)	8 (50.0%)	55 (59.8%)	ns	
Acute GVHD grade II	33 (30.6%)	6 (37.5%)	27 (29.3%)	ns	
Acute GVHD III-IV	12 (11.1%)	2 (12.5%)	10 (10.9%)	ns	
Chronic GVHD limited	10 (10.9%)	0 (0%)	10 (9.3%)	ns	
Chronic GVHD extensive	49 (45.4%)	7 (43.8%)	42 (45.7%)	ns	
Hb at 12 months (µmol/L) mean (range)	8.3 (5.0-10.5)	8.0 (5.0-10.4)	8.6 (5.8-10.5)	P=0.036	
Cyclosporine trough Level >400 ng/ml	54 (50.9%)	8 (50.0%)	46 (51.1%)	ns	
Outcome				ns	
Alive	86 (79.6%)	14 (87.5%)	72 (73.3%)		
Dead	22 (20.4%)	2 (12.5%)	20 (21.7%)		

Abbreviations: TBI = total body irradiation; ATG = antithymocyte globulin; GFR-1 month = glomerular filtration rate 1 month prior to SCT in mL/min/1.73 m^2. Median (range); Creatinine-1 months = creatinine 1 month prior to SCT in µmmol/L. Median (range); CMV = cytomegalovirus; ICU = intensive care unit; GVHD = graft-versus-host disease; Hb = hemoglobin in mmol/L. Median (range).

patients who develop CKD despite nonmyeloablative conditioning regimen are of older age and/or have more comorbidities.

The strongest risk factor for the development of CKD was lower estimated GFR 1 month prior to SCT in multivariate analysis. This was similar to our previous study regarding CKD after myeloablative SCT.[12] Also in community-based population studies, mildly reduced GFR is a predictor for the development of kidney disease.[32] Suboptimal kidney function therefore seems to predispose for CKD. Critical evaluation of kidney function before SCT and adequate treatment of risk factors for CKD (eg hypertension and diabetes) seems a logical approach for these vulnerable patients.

A second risk factor for CKD was older age in univariate analysis. This was also found in studies on CKD after myeloablative SCT.[5,12] Cross-sectional community studies showed progressive decline in renal function with aging.[25,32] Renal aging is a natural phenomenon with a course that is dependent on a combination of genetic and environmental factors.[33] The nonmyeloablative conditioning before SCT, and the immunesuppression regimen or infection prophylaxis used posttransplantation, are candidate factors that progress the renal aging process.

A third risk factor for CKD was female sex in univariate analysis. This was also found in our earlier study on CKD after myeloablative SCT.[12] Also, studies in general population showed a higher incidence of CKD for women than for men,[31,32] a reason to modify the cutoff value for CKD for women in 1 study.[3] Awareness of CKD in women is lower, which might be caused by overlooking CKD in older women, who often have a serum creatinine that is in the normal range for younger individuals.[34]

Acute renal failure after nonmyeloablative SCT was not associated with increased risk for CKD, in contrast to previous studies.[11,26] Our system of frequent monitoring of serum creatinine and performing dose reductions of nephrotoxic medication in the case of an acute rise in creatinine might prevent irreversible renal damage in those patients. Cyclosporine use did not influence the occurrence of CKD. It is known that chronic cyclosporine use contributes to CKD in patients after heart and lung transplantation.[35] Acute cyclosporine injury is usually reversible,[36] but there is also evidence that chronic cyclosporine nephrotoxicity has reversible components.[37] Using cyclosporine only for restricted periods and monitoring of trough levels seems to be a safe method to prevent cyclosporine nephrotoxicity in patients after SCT. Also, cGVHD was not a risk factor for CKD, in contrast to other studies.[4,11,26] The postulated independent role in development of CKD for cGVHD with chronic inflammation and cyclosporine use could therefore not be confirmed by our study.[17]

No patient developed SCT nephropathy, which is in line with results of a previous study after nonmyeloablative SCT.[26] The low dose of TBI in nonmyeloablative SCT in comparison with myeloablative SCT may account for this.

The mechanisms by which CKD is caused after nonmyeloablative SCT are still unknown, but a thrombotic microangiopathic syndrome caused by radiation is very unlikely. A combination of factors (eg chemotherapy, TBI, nephrotoxic medication and GVHD) might cause CKD in susceptible patients because they are of older age, have female sex or, most important, have decreased kidney function.

Patients with CKD had slightly lower Hb levels compared to patients without CKD. This is as expected, and underscores the importance of identifying patients with GFR < 60 ml/min/1.73 m^2 because of increased morbidity under this cutoff value.[10]

Finally, survival was not influenced by CKD in this cohort. The reason for this might be that follow-up was still too short for development of late complications of CKD.

In conclusion, CKD is a frequent complication after nonmyeloablative SCT. Women, patients above 50 years of age and patients with slightly decreased kidney function pretransplant have the greatest risk of development of CKD. Multiple factors are thought to influence the development of CKD, but the exact mechanism needs further study.

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7

Successful outcome after nonmyeloablative allogeneic hematopoietic stem cell transplantation in patients with renal dysfunction

Sabina Kersting and Leo F. Verdonck

Department of Hematology, University Medical Center Utrecht, The Netherlands

Submitted

Abstract

Nonmyeloablative allogeneic hematopoietic stem cell transplantation (HSCT) is a transplantation approach that enables patients with comorbid conditions to undergo allogeneic HSCT. We investigated the outcome of patients with reduced renal function as a single comorbidity before HSCT.

Fifteen patients with a glomerular filtration rate (GFR) of < 60 mL/min/1.73 m^2 were matched on sex, age and type of transplant to 30 controls with normal renal function. All patients received a nonmyeloablative HSCT with fludarabine and/or total body irradiation (TBI) conditioning. Graft-versus-host disease (GVHD) prophylaxis consisted of mycophenolate mofetil (MMF) and cyclosporine. Data on renal function, cyclosporine dose, cyclosporine trough levels, hypertension and GVHD were collected.

Of the 15 patients with impaired renal function, 8 patients (53%) improved or stabilized to a GFR ≥ 60 mL/min/1.73 m^2 at last follow-up. Five patients (33%) developed chronic kidney disease stage 3 (GFR < 60 mL/min/1.73 m^2) compared to 5 patients (17%) in the control group (P = 0.031). There was no difference in survival between cases and controls. Furthermore, there were no differences in complications after HSCT and cyclosporine dose and trough levels were similar between cases and controls.

Nonmyeloablative HSCT can be safely offered to patients with mildly reduced renal function. Cyclosporine can be administered at the same dose as patients without renal dysfunction, as long as cyclosporine trough levels and creatinine are monitored and dose adjustments are made if necessary.

Introduction

Chronic kidney disease is a severe complication of allogeneic hematopoietic stem cell transplantation (HSCT). An important risk factor for chronic kidney disease is lower glomerular filtration rate (GFR) before HSCT.[1] Also in studies on renal function after solid organ transplantation, impaired renal function pretransplant predisposes for end-stage renal disease.[2,3] Moreover, renal dysfunction before HSCT is one of the risk factors of the hematopoietic cell transplantation-specific co-morbidity index[4] and the Pretransplantation Assessment of Mortality score,[5] that predict survival after HSCT. No studies have been performed on the outcome of patients with renal dysfunction as a single comorbidity before allogeneic HSCT.

Nonmyeloablative allogeneic HSCT is a transplantation approach that enables patients with comorbid conditions to undergo allogeneic HSCT who otherwise are not suitable for allogeneic myeloablative HSCT.[6] Patients with impaired renal function can therefore be candidates for nonmyeloablative HSCT. Use of immunesuppressive drugs like mycophenolate mofetil (MMF) and cyclosporine are very important to prevent non-engraftment and graft-versus-host disease (GVHD).[6] Cyclosporine is well known for its nephrotoxicity and the major cause for chronic kidney disease after heart and lung transplantation.[7] It is not known whether cyclosporine can be safely used as an immunesuppressive agent in patients with impaired renal function before HSCT.

The aim of the present study was to assess the outcome of patients with mildly reduced renal function before nonmyeloablative HSCT.

Patients and Methods

Patients

Between September 1, 2001 and October 1, 2005, nonmyeloablative HSCT was performed in 150 adults, aged 20-69 years, at the Department of Hematology of the University Medical Center Utrecht. Of these patients, 15 had mildly reduced renal function within 1 month prior to HSCT with a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 using the simplified Modification of Diet in Renal Disease (MDRD) Study prediction equation: GFR = 186,3 x (serum creatinine)$^{-1.154}$ x age$^{-0.203}$ x (0.742 for women).[8] Two control subjects with normal renal function for every patient with impaired renal function were selected from the cohort and matched on sex, age and type of transplantation. Patients gave informed consent and were treated according to clinical protocols approved by the local ethics review board.

Methods

Of the 15 patients with mildly reduced renal function and 30 controls, data were collected and analyzed retrospectively using a database and patient records through December 1, 2007. The following baseline variables were noted: sex, age, history of autologous transplantation, history of hypertension (defined as a blood pressure ≥ 140/80 mmHg or receiving antihypertensive medication), diagnosis of hematologic disease, malignancy risk (low risk malignancy: patients with acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase and untreated severe aplastic anemia [SAA]; high risk malignancy: all other hematologic diseases), type of transplant (matched related donor, partially matched related donor, matched unrelated donor) and conditioning regimen. Serum creatinine was noted at 1 month prior to HSCT, at the day of HSCT, monthly during the first year, at 18 months and 24 months and thereafter annually. Renal function was assessed with the simplified MDRD Study prediction equation at 1 month prior to HSCT, day of HSCT, monthly during the first year, at 18 months and 24 months and thereafter annually. Chronic kidney disease was defined according to the K/DOQI definition of kidney disease. Stage 3 chronic kidney disease was an estimated GFR < 60 mL/min/1.73 m^2, stage 4 chronic kidney disease was a GFR < 30 mL/min/1.73 m^2 and stage 5 chronic kidney disease a GFR < 15 mL/min/1.73 m^2 or need for dialysis.[8]

Acute renal failure grade 2 was defined as a > two-fold rise in serum creatinine from baseline value if it occurred within 100 days after HSCT.[9]

Nephrotic syndrome was defined as a urinary protein excretion > 3.5 g/24 hr and hypoalbuminemia with plasma levels < 3g/dl.

The following variables posttransplantation were registered: acute and chronic GVHD (aGVHD, cGVHD), hypertension, cyclosporine dose the first 3 months, cyclosporine trough levels, duration of cyclosporine use, and survival.

HSCT procedure

The nonmyeloablative conditioning regimen before HSCT consisted of fludarabine (30 mg/m^2/day for 3 days) followed by total body irradiation (TBI) of 200 cGy or TBI of 200 cGy alone given in the tandem autologous and allogeneic HSCT. The graft was infused after TBI on day 0. In recipients of a histocompatibility leukocyte antigen (HLA)-matched unrelated donor or a single HLA-antigen mismatched family donor, antithymocyte globulin (Rabbit ATG, Thymoglobulin™,Genzyme, Cambridge. MA) was given before fludarabine was infused, at a dose of 2 mg/kg/day for 4 days.

All patients received GVHD prophylaxis orally with cyclosporine and MMF. Cyclosporine was started on day -3 at 4.5 mg/kg twice daily and continued until

day +84 or +120 followed by tapering if no GVHD was present. Dose adjustments were made to keep cyclosporine trough levels between 200 ng/mL and 400 ng/mL. Moreover, cyclosporine dose was lowered when creatinine rise was caused by cyclosporine, at the discretion of the physician. MMF was started 5 hours after graft infusion at 45 mg/kg/day with a maximum dose of 3 g/day until day +28 or +84, followed by tapering if no GVHD was present. GVHD was diagnosed according to the Seattle criteria.[10] aGVHD grade I was treated with topical corticosteroids. aGVHD grade II or higher was treated with high-dose systemic corticosteroids. Limited cGVHD was not treated and extensive cGVHD was treated with cyclosporine, systemic or topical corticosteroids, MMF or a combination of these drugs.
Infection prevention consisted of ciprofloxacin and fluconazole, given orally, until granulocyte counts exceeded 500 cell/µl. Co-trimoxazol 480 mg, twice daily, was given for 15 months and valacyclovir 500 mg, twice daily, was given for 12 months, both orally.

Statistical analysis

Continuous variables are displayed as the median, with range in parentheses. For dichotomous variables, the frequency of occurrence is given along with the corresponding percentage. For comparison of characteristics between patients with or without renal dysfunction at baseline, chi-square test or Fisher's exact test was used to compare proportions, and two-sided Student's t-test to compare continuous outcomes.
Kaplan-Meier survival curves were made for overall survival (OS). Curves were compared with log-rank test. All P-values were two-sided and a value of <0.05 was considered statistically significant. Analysis was performed using SPSS version 14.0 (SPSS Inc, Chicago II, USA).

Results

Of the 150 patients reviewed, 15 patients had a GFR < 60 ml/min/1.73 m^2 before HSCT. Characteristics of this group and their controls are shown in Table 1.
Renal dysfunction was caused by light chain deposition disease in multiple myeloma in 1 patient, and in the rest of the patients there was no established cause. Treatment with antithymocyte globulin and cyclosporine for SAA or hypoplastic myelodysplastic syndrome might have caused renal dysfunction in 4 patients. Eight patients (53%) improved or stabilized to a GFR ≥ 60 mL/min/1.73 m^2 at last follow-up, 5 patients (33%) developed chronic kidney disease stage 3 (GFR < 60 mL/min/1.73 m^2) and 2 patients (13%) had a GFR < 30 mL/min/1.73 m^2 just before they died from relapse of lymphoma and chronic lymphocytic leukemia. Of the 5 patients (33%)

Table 1. Comparison of patients with renal dysfunction and controls

	Renal dysfunction	Normal renal function	P-value
Sex			ns
Male	6 (40%)	12 (40%)	
Female	9 (60%)	18 (60%)	
Age (range)	59 (37-67)	59 (21-65)	ns
Type of transplant			ns
Matched related donor	11 (73%)	22 (73%)	
Partially matched related donor	0 (0%)	1 (3%)	
Matched unrelated donor	4 (27%)	7 (23%)	
Mismatch	0 (0%)	3 (10%)	
Diagnosis			
Acute myelogenous leukemia	4 (27%)	8 (27%)	
Chronic myelogenous leukemia	0 (0%)	2 (7%)	
Severe aplastic anemia	1 (7%)	0 (0%)	
Multiple myeloma	1 (7%)	11 (37%)	0.038
Non Hodgkin lymphoma	3 (20%)	4 (13%)	
Chronic lymphocytic leukemia	2 (13%)	3 (10%)	
Myelodysplastic syndrome	4 (27%)	0 (0%)	
Myelofibrosis	0 (0%)	1 (3,3%)	
Hodgkin lymphoma	0 (0%)	1 (3,3%)	
Risk			ns
Low risk malignancy	2 (13%)	8 (27%)	
High risk malignancy	13 (87%)	22 (73%)	
Previous autologous	1 (7%)	12 (40%)	0.034
Previous hypertension	6 (40%)	11 (37%)	ns
Conditioning			ns
Fludarabine/TBI	9 (60%)	14 (47%)	
Fludarabine/TBI/ATG	5 (33%)	8 (27%)	
TBI	1 (7%)	8 (27%)	
Renal function at day 0			
Creatinine (µmoll/L) median (range)	115 (63-178)	75 (50-102)	<0.001
Estimated GFR (ml/min/1.73 m^2) MDRD (range)	56 (35-88)	82 (61-124)	<0.001
Complications			ns
Acute renal failure	2 (13%)	10 (33%)	
Hypertension within 100 days	6 (40%)	7 (23%)	
aGVHD grade 0-I	7 (47%)	16 (53%)	
aGVHD grade II	8 (53%)	11 (37%)	
aGVHD III-IV	0 (0%)	3 (10%)	
cGVHD limited	2 (13%)	2 (7%)	
cGVHD extensive	5 (33%)	14 (47%)	
Nephrotic syndrome	1 (7%)	1 (3%)	
Hypertension at last follow-up	5 (36%)	12 (40%)	
Chronic kidney disease			0.031
Chronic kidney disease stage 3	5 (33%)	5 (17%)	
Chronic kidney disease stage 4	2 (13%)	0 (0%)	
Renal function at last follow-up			
Creatinine (µmoll/L) median (range)	96 (66-231)	79,5 (43-124)	0.018
Estimated GFR (ml/min/1.73 m^2) MDRD (range)	60 (26-84)	78 (40-151)	0.004
Outcome			
Follow-up living patients in months (range)	37 (26-55)	42 (27-62)	ns
Survival	10 (67%)	21 (70%)	ns

Abbreviations: TBI = total body irradiation; ATG = antithymocyte globulin; GFR = glomerular filtration rate, MDRD = Modification of Diet in Renal Disease Study prediction equation; aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease

who died, 3 died because of relapse of the hematologic disease, 1 died of tuberculosis and 1 died after an acute event with dyspnoea and hypotension. None of the deaths were related to renal dysfunction.

For each patient with renal dysfunction before HSCT, 2 patients from the cohort with normal renal function were matched for sex, age and type of transplant (Table 1). In the control group, there were significantly more patients with multiple myeloma ($P = 0.038$) and previous autologous transplantation ($P = 0.034$). There were no differences in previous hypertension, malignancy risk or conditioning regimen between patients with renal dysfunction and the control group. Creatinine and GFR at time of HSCT was significantly different between patients with renal dysfunction and controls ($P < 0.001$).

In the control group, 5 patients (17%) developed chronic kidney disease stage 3 (GFR < 60 mL/min/1.73 m^2) and no patient developed severe renal dysfunction. This was significantly less than for the patients with renal dysfunction before HSCT ($P = 0.031$). There was no difference in occurrence of acute renal failure, hypertension, aGVHD, cGVHD or nephrotic syndrome in patients with renal dysfunction or controls. There was also no difference in cyclosporine dose or cyclosporine trough levels or duration of cyclosporine treatment between patients with renal dysfunction and controls (Table 2).

Follow-up was 37 months (range 26-55) for patients with renal dysfunction and 42 months (27-62) for controls. OS was 67% for patients with renal dysfunction and 70% for controls. This was not significantly different.

Table 2. Comparison of cyclosporine dose, trough levels and duration between patients with renal dysfunction and controls

	Renal dysfunction (range)	Normal renal function (range)	P-value
First cyclosporine trough level (ng/ml)	260 (30-930)	280 (70-240)	ns
Second cyclosporine trough level (ng/ml)	280 (70-950)	330 (130-360)	ns
Third cyclosporine trough level (ng/ml)	230 (60-650)	270 (70-520)	ns
Cyclosporine maximal trough level (ng/ml)	470 (50-940)	395 (160-660)	ns
Cyclosporine dose day 0 b.i.d. (mg)	350 (100-500)	350 (200-550)	ns
Cyclosporine dose 2 weeks b.i.d. (mg)	200 (100-350)	200 (150-400)	ns
Cyclosporine dose 1 month b.i.d. (mg)	175 (100-300)	175 (100-300)	ns
Cyclosporine dose 2 months b.i.d. (mg)	137,5 (75-300)	125 (0-250)	ns
Cyclosporine dose 3 months b.i.d. (mg)	100 (50-300)	100 (0-250)	ns
Cyclosporine duration in days	182 (105-561)	187 (40-1501)	ns

Discussion

In this study of 15 patients with mildly reduced renal function before nonmyeloablative allogeneic HSCT, more than half of patients had improvement of renal function after HSCT, despite regular treatment with cyclosporine. Furthermore, 33% developed chronic kidney disease stage 3 (GFR < 60 ml/min/1.73 m^2), which occurred in 17% of the control group with normal renal function pretransplant. No patient progressed to end-stage renal disease. Also, mortality was not increased compared to the control group. This suggests that nonmyeloablative HSCT is a safe option for patients with mildly reduced renal function before HSCT.

Surprisingly, there was no difference in cyclosporine dose and trough levels between patients with renal dysfunction and controls. Cyclosporine is metabolized by the liver and trough levels are not influenced by renal dysfunction.[11] However, one would expect that patients with renal dysfunction are more susceptible for rise in serum creatinine and hypertension caused by cyclosporine, which would lead to adjustment of the dose by the physician. This was apparently not the case, because trough levels and cyclosporine dose were not different between patients with renal dysfunction and controls, and the incidence of acute hypertension was similar. It is known from studies in patients after allogeneic HSCT and heart transplantation, that cyclosporine trough levels often do not correlate with the occurrence of acute renal failure.[9,12-16] Nephrotoxicity of cyclosporine seems to be the result of individual toxic effects of cyclosporine and not correlated to pretransplant creatinine.[15] This suggests that cyclosporine can be administered safely in patients with renal dysfunction, as long as cyclosporine trough levels and creatinine are monitored and dose adjustments will be made similar as in patients without renal dysfunction.

A limitation of this study is the retrospective nature and the small sample size. Therefore it was not possible to match on all variables, however, the controls were matched for important risk factors for chronic kidney disease; female sex and older age.[1,17,18] In the control group there were more patients with multiple myeloma and previous autologous transplantation. Although multiple myeloma can have renal disease at presentation, it is not a risk factor for chronic kidney disease after HSCT.[1] Autologous transplantation was a risk factor for chronic kidney disease after nonmyeloablative HSCT in one study,[19] but in our previous study we could not confirm this.[20] Therefore, we don't think these difference between the cases and the controls have influenced the results. The incidence of chronic kidney disease of 17% in the control group is comparable to the 15% in our previous study.[20] This confirms that the control group fits well.

In conclusion, nonmyeloablative HSCT can be safely offered to patients with mildly reduced renal function. Cyclosporine can be administered at the same dose as patients without renal dysfunction, as long as cyclosporine trough levels and creatinine are monitored and dose adjustments are made if necessary.

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8

Summary, Conclusions and Recommendations

Summary and Conclusions

Allogeneic stem cell transplantation (SCT) is a widely accepted approach for malignant and nonmalignant hematopoietic diseases. Unfortunately complications can occur because of the treatment, leading to treatment-related mortality (TRM). These complications can occur early after SCT (within 100 days) or late after SCT (after day 100). We studied kidney dysfunction after allogeneic SCT in 2 cohorts of patients: 1 cohort treated with myeloablative conditioning regimen and 1 cohort treated with nonmyeloablative conditioning regimen.

In **chapter 2** we describe acute renal failure in patients that received myeloablative SCT. Acute renal failure was defined as > doubling in serum creatinine from time of SCT. We found that almost half of patients developed acute renal failure at a median of 40 days after SCT. Four patients (1.1%) required dialysis. A risk factor for acute renal failure was previous hypertension. Admission to the intensive care unit, occurring in 4,4% of patients, was associated with acute renal failure.
Overall survival was 75% after 6 months. Survival was 68% in patients with acute renal failure. This was attributable to severe complications being associated with acute renal failure (eg admission to the intensive care unit, veno-occlusive disease, severe graft-versus-host disease [GVHD] and thrombotic thrombocytopenic purpura [TTP]). In patients without these severe complications survival was similar for patients with and without acute renal failure. Acute renal failure not associated with complications is most probably caused by cyclosporine, although we could not confirm this with cyclosporine trough levels.

In **chapter 3** we describe acute renal failure in patients that received nonmyeloablative SCT. Acute renal failure was defined as > doubling in serum creatinine from time of SCT. We found that one-third of patients developed acute renal failure at a median of 37 days after SCT. None of the patients required dialysis, but 9% had > tripling of serum creatinine. Risk factors for acute renal failure were previous autologous transplantation, the absence of vascular disease, and lower serum creatinine at time of SCT. Severe acute GVHD (aGVHD) was associated with acute renal failure.
Overall survival was 84% after 6 months. Survival was 70% in patients with acute renal failure. This was attributable to relapse mortality and complications with high mortality in patients with > tripling in serum creatinine. In patients with doubling of serum creatinine, there was no decreased survival compared to patients with mild acute renal failure or no acute renal failure. Acute renal failure not associated with complications is most probably caused by cyclosporine, although, again, we could not confirm this with cyclosporine trough levels.

Concluding from these 2 studies, acute renal failure is a frequent complication after SCT occurring less frequent in nonmyeloablative than in myeloablative SCT. The absolute changes required for doubling of serum creatinine is lower for persons with lower creatinine. Patients with lower creatinine will therefore meet the definition of acute renal failure sooner. This is most probably the reason for lower creatinine as a risk factor for acute renal failure in the study of the nonmyeloablative cohort. An explanation for the discrepancy between clinical impression and statistical analysis of the effect of cyclosporine on renal function may be the variability in cyclosporine trough levels within a patient and the transient effect of cyclosporine on renal function.
Although mortality is higher in patients with acute renal failure, this is not caused by acute renal failure per se, but by complications or relapse with high mortality associated with more severe acute renal failure. Acute renal failure in the absence of a complication or relapse is most probably caused by cyclosporine and these patients have similar survival as patients without acute renal failure. However this is only true if cyclosporine is adequately monitored and dose adjustments made depending on cyclosporine trough levels and/or rise in creatinine as we did in our center.

In **chapter 4** we describe 6 cases of SCT nephropathy from the myeloablative SCT cohort. SCT nephropathy, also known as bone marrow transplantation nephropathy, conditioning-associated HUS or radiation nephritis is a microangiopathic condition that can lead to chronic kidney disease. It is characterized by an increase in creatinine, microangiopathic hemolytic anemia, and hypertension, occurring typically 6-12 months after SCT. The differences with TTP are, that TTP usually develops within 3 months after SCT and often occurs with other complications, whereas SCT nephropathy is a late complication and occurs without other complications.
We found that in 6 patients with SCT nephropathy, 3 patients had an acute decline in kidney function, 1 had a more gradual decline in kidney function and 2 patients had an initial decline followed by stabilization at a reduced glomerular filtration rate (GFR). Two patients developed end-stage kidney disease, 3 patients developed severe kidney disease stage 4 and 1 patient died of SCT nephropathy. Treatment with ACE inhibition stabilized kidney function in only 1 of 5 patients. As expected, there was no influence of nephrotoxic drugs on the development of this syndrome and proteinuria was absent.

In **chapter 5** we describe chronic kidney disease after myeloablative SCT. Chronic kidney disease was defined as a GFR of < 60 mL/min/1.73 m^2. We found a cumulative incidence of chronic kidney disease of 20% after 5 years. Only 2 patients required dialysis. Pretransplant risk factors for chronic kidney disease were lower

GFR at SCT, female sex and higher age. Of patients with suboptimal kidney function before SCT, more than half progressed to chronic kidney disease. The occurrence of hypertension after SCT was associated with chronic kidney disease. Acute renal failure was not associated with chronic kidney disease and we could not find a relationship between cyclosporine and chronic kidney disease. SCT nephropathy was the cause of chronic kidney disease in only 6 patients, but was the cause of end-stage kidney disease in both patients that required dialysis.
Overall survival was about 60% after 5 years. There was no significant difference in survival between patients with and without chronic kidney disease.

In **chapter 6** we describe chronic kidney disease after nonmyeloablative SCT. Chronic kidney disease was defined as a GFR of < 60 mL/min/1.73 m^2. We found a cumulative incidence of chronic kidney disease of 22% after 4 years. None of the patients required dialysis. Pretransplant risk factors for chronic kidney disease were lower GFR, female sex and higher age. Of patients with suboptimal kidney function before SCT, a quarter progressed to chronic kidney disease. Acute renal failure was not associated with chronic kidney disease, and we could not find a relationship between cyclosporine and chronic kidney disease. There were no cases with SCT nephropathy.
Overall survival was 66% after 4 years. There was no significant difference in survival between patients with and without chronic kidney disease.

Concluding from these 3 studies, chronic kidney disease is a frequent complication after SCT. SCT nephropathy is a rare syndrome that can occur when high dose total body irradiation (TBI) is given in the myeloablative conditioning regimen. However it is a very important syndrome, because it is the only cause of end-stage kidney disease that can develop early after SCT.
Chronic kidney disease not caused by SCT nephropathy occurs more in patients with lower GFR before SCT. Female and older patients are more susceptible for decline in kidney function. Acute renal failure caused by acute cyclosporine toxicity is usually reversible and does not lead to chronic kidney disease. Because cyclosporine is only used for restricted time periods, chronic cyclosporine toxicity is not a likely cause of chronic kidney disease in SCT patients. The mechanisms for chronic kidney disease are not clear, but a combination of factors (eg chemotherapy, TBI, nephrotoxic medication, and GVHD) might cause chronic kidney disease in susceptible patients with a suboptimal kidney function before SCT.
Survival was not influenced by chronic kidney disease, but the reason for this might be that follow-up was too short for development of late complications of kidney disease, like cardiovascular disease. Moreover, renal function declines with age and

chronic kidney disease can progress to end-stage kidney disease in both cohorts with longer follow-up. Since no specific interventions for risk factors are possible, management of chronic kidney disease according to the National Kidney foundation Kidney Disease Outcomes Quality Initiative guidelines hopefully slows progression of chronic kidney disease to kidney failure.

In **chapter 7** we describe the outcome of 15 patients with renal dysfunction before nonmyeloablative SCT compared to patients with normal renal function before SCT. Renal dysfunction was defined as a GFR of < 60 mL/min/1.73 m^2 within 1 month prior to SCT. We found that 33% of patients with renal dysfunction developed chronic kidney disease compared to 17% in controls. None of the patients required dialysis. Moreover, more than half of patients with renal dysfunction had improvement of kidney function following SCT. There was no difference between both cohorts in complications after SCT. Cyclosporine dose, duration and trough levels were similar for patients with renal dysfunction and with normal renal function. Survival was the same for patients with renal dysfunction and controls.

Concluding from this last study, nonmyeloablative SCT can be safely offered to patients with mildly reduced renal function. Cyclosporine can be administered at the same dose as patients without renal dysfunction, as long as cyclosporine trough levels and creatinine are monitored and dose adjustments are made if necessary. For patients who do develop chronic kidney disease, management according to the National Kidney foundation Kidney Disease Outcomes Quality Initiative guidelines should be applied.

Recommendations

All patients who are eligible for SCT should be monitored for renal function. In case of a glomerular filtration rate (GFR) between 30-59 ml/min/1.73 m^2 nonmyeloablative SCT can be offered. Immunesuppression treatment can be similar for all patients (Chapter 6).
Cyclosporine levels and creatinine should be monitored after SCT and dose adjustments made in case of too much rise in creatinine, or toxic trough level of cyclosporine. With this approach, rise in creatinine will be tempory and will not lead to chronic kidney disease or impaired survival (Chapter, 2, Chapter 3, Chapter 5 and Chapter 6).
If a rise in creatinine suddenly occurs in a patient with anemia and hypertension, who has had a myeloablative SCT > 3 months ago, SCT nephropathy has developed

and treatment with ACE inhibition should be started. These patients have a very high risk for progression to end-stage kidney disease and referral to a nephrologist should be considered. Anemia in these patients can be treated with low dose erytropoietin (Chapter 4).
In all SCT patients yearly monitoring of serum creatinine, glucose, urine microalbumin/creatinine ratio and bloodpressure should be performed. In patients with a calculated GFR < 60 ml/min/1.73 m^2, monitoring should be performed more often and consultation of a nephrologist should be considered. Diabetes and hypertension should be strictly treated. When the patients does not use cyclosporine, hypertension should be treated with an ACE inhibitor, otherwise a calcium-antagonist is first choice. ACE inhibition should also be started in case of microalbinuria. Other risk factors for cardiovascular disease should be monitored and treated.

Nederlandse Samenvatting

Samenvatting en Conclusies

Leukemie, de ziekte van Kahler en lymfklierkanker zijn voorbeelden van kwaadaardige ziekten van het beenmerg of de lymfklieren waarbij het afsluitende deel van de behandeling kan bestaan uit een stamceltransplantatie (ook wel beenmergtransplantatie genoemd). Deze behandeling kan ook gegeven worden bij andere beenmergziekten. Bij een allogene stamceltransplantatie worden stamcellen van een donor gegeven aan een patiënt, bij een autologe stamceltransplantatie worden stamcellen van de patiënt zelf teruggegeven aan de patiënt. Deze stamcellen kunnen verkregen worden uit bloed of beenmerg.

De allogene stamceltransplantatie-procedure bestaat uit het toedienen van de stamcellen van een donor aan een patiënt die voorbehandeld is met chemotherapie en/of bestraling van het gehele lichaam. De voorbehandeling in combinatie met de stamcellen zorgen ervoor dat het beenmerg van de patiënt wordt uitgeschakeld en vervangen wordt door beenmerg dat bestaat uit donorcellen. Deze donorcellen zorgen ervoor dat de ziekte verder bestreden wordt of dat de ziekte minder kans heeft om terug te komen.

Er zijn twee allogene stamceltransplantatie-procedures mogelijk in ons ziekenhuis: één waarbij met hoge dosering chemotherapie en lichaamsbestraling het beenmerg van de patiënt zo goed als vernietigd wordt en in korte tijd vervangen wordt door beenmerg van donorcellen (myeloablatieve stamceltransplantatie) en één waarbij met lagere dosering chemotherapie en/of lichaamsbestraling het beenmerg van de patiënt zodanig beschadigd raakt dat de donorcellen het volledige nieuwe beenmerg zullen gaan vormen binnen enkele weken tot maanden (niet-myeloablatieve stamceltransplantatie).

Helaas kunnen er complicaties ontstaan als gevolg van de stamceltransplantatie. De belangrijkste complicatie is een omgekeerde afstotingsreactie (graft-versus-host disease) waarbij de donorcellen het lichaam van de patiënt als "vreemd" herkennen. Dit kan leiden tot levensbedreigende diarree, leverproblemen en huidproblemen. Een ander groot probleem is de verminderde afweer van de patiënt, waardoor infecties kunnen optreden. Verder kan er schade optreden aan verschillende organen.

Dit proefschrift beschrijft het onderzoek naar nierfunctiestoornissen bij patiënten die een allogene stamceltransplantatie ondergingen in het UMC Utrecht. Dit onderzoek werd gedaan in 2 grote groepen patiënten: een groep die een myeloablatieve stamceltransplantatie had ondergaan en een groep die een niet-myeloablatieve stamceltransplantatie had ondergaan.

Nierfunctiestoornissen kunnen acuut en tijdelijk zijn (binnen 100 dagen na de stamceltransplantatie) of chronische nierziekten geven (blijvende nierfunctiestoornis vanaf 3 maanden na de stamceltransplantatie). Het gevaar van acute nierfunctiestoornissen is dat het kan leiden tot ontregeling van de water-en zouthuishouding. Dit kan in ernstige gevallen levensbedreigende gevolgen hebben met noodzaak tot tijdelijke dialyse en het kan leiden tot blijvende nierschade. Het gevaar van chronische nierziekten is dat ze een verhoogd risico geven op hart-en vaatziekten, botproblemen, bloedarmoede en een verminderd welbevinden. Bovendien kunnen chronische nierziekten leiden tot eindstadium nierfalen met noodzaak tot permanente dialyse.
De nierfunctiestoornis werd bij de onderzoeksgroep onderzocht door in het bloed naar het eiwit creatinine te kijken, een maat voor de nierfunctie. Bij goed functionerende nieren is het creatinine in het bloed laag, bij nierfalen stijgt het creatinine. Met een formule die rekening houdt met geslacht, leeftijd en creatinine kan een schatting gemaakt worden van de snelheid waarmee de nier het bloed filtert, de glomerulaire filtratie snelheid. Een hoge waarde is een goede nierfunctie, bij verslechtering van de nierfunctie daalt de waarde.

In **hoofdstuk 2** wordt acuut nierfalen bij patiënten die een myeloablatieve stamceltransplantatie hadden ondergaan beschreven. Het bleek dat meer dan de helft van de patiënten acuut nierfalen ontwikkelden na gemiddeld 40 dagen na de stamceltransplantatie. Vier patiënten (1.1%) hadden dialyse nodig. Een risicofactor voor acuut nierfalen was een voorgeschiedenis van hoge bloeddruk. Ook kwam acuut nierfalen vaker voor bij patiënten die opgenomen waren op de intensive care unit, wat nodig was bij 4.4% van de patiënten.
Driekwart van alle patiënten was nog in leven na 6 maanden, maar de overleving was minder bij patiënten met acuut nierfalen. Dit was toe te schrijven aan andere ernstige complicaties die de patiënten hadden ten tijde van het acuut nierfalen. Als de patiënten niet deze ernstige complicaties hadden, was de overleving gelijk voor de patiënten met en zonder acuut nierfalen. Acuut nierfalen zonder de aanwezigheid van andere complicaties wordt waarschijnlijk veroorzaakt door het medicijn cyclosporine, een afweer onderdrukkend medicijn dat alle stamceltransplantatie patiënten de eerste periode na de stamceltransplantatie krijgen. We konden dit echter niet aantonen met aanwezigheid van te hoge bloedspiegels van dit medicijn.

In **hoofdstuk 3** wordt acuut nierfalen bij de patiënten die een niet-myeloablative stamceltransplantatie hadden ondergaan beschreven. Het bleek dat eenderde van de

patiënten acuut nierfalen ontwikkelde na gemiddeld 37 dagen na de stamceltransplantatie. Geen van de patiënten had ernstig nierfalen waarvoor dialyse nodig was, maar 9% had vrij ernstig nierfalen. Risicofactoren voor acuut nierfalen waren een eerdere autologe stamceltransplantatie, geen verleden van hart-en vaatziekten en een laag creatinine (goede nierwaarde) op het tijdstip van de stamceltransplantatie. De patiënten met een ernstige acute graft-versus-host disease hadden vaker acuut nierfalen dan de andere patiënten.
Na 6 maanden was 84% van alle patiënten nog in leven, maar de overleving was minder bij de patiënten met acuut nierfalen. Dit was toe te schrijven aan overlijden door terugkeer van de beenmergziekte en overlijden aan complicaties bij de patiënten met vrij ernstig nierfalen. De overleving van de andere patiënten met acuut nierfalen en de patiënten zonder acuut nierfalen was gelijk. Acuut nierfalen zonder de aanwezigheid van andere complicaties werd waarschijnlijk veroorzaakt door het medicijn cyclosporine, alhoewel de bloedspiegels wederom niet verhoogd waren.

Uit deze 2 studies kan geconcludeerd worden dat acuut nierfalen een vaak voorkomende complicatie is na een stamceltransplantatie, die vaker voorkomt bij een myeloablatieve dan een niet-myeloablatieve stamceltransplantatie. Hoewel de patiënten met acuut nierfalen vaker dood gingen, is dit niet het gevolg van het acuut nierfalen op zich, maar het gevolg van de complicaties of een terugkeer van de beenmergziekte die gepaard ging met acuut nierfalen. Acuut nierfalen zonder complicaties of recidieven wordt waarschijnlijk veroorzaakt door cyclosporine. Deze patiënten hebben gelijke overlevingskansen als de patiënten zonder nierfalen. Dit is echter alleen waar als de cyclosporine dosering goed in de gaten wordt gehouden en wordt aangepast als de bloedspiegels te hoog zijn of als het creatinine te veel stijgt, zoals wij gedaan hebben in het UMC Utrecht.

In **hoofdstuk 4** worden 6 gevallen van stamceltransplantatie nefropathie uit de myeloablatieve stamceltransplantatie patiënten groep beschreven. Stamceltransplantatie nefropathie, dat ook bekend staat als beenmergtransplantatie nefropathie of bestralings nefritis is een syndroom waarbij de bloedplaatjes in de kleine bloedvaten van de nier samenklonteren en de rode bloedcellen kapot gaan. Het syndroom dat ontstaat tussen 6 en 12 maanden na de stamceltransplantatie kenmerkt zich door een stijging van het creatinine, bloedarmoede en hoge bloeddruk.
Het bleek dat bij de 6 patiënten met stamceltransplantatie nefropathie 3 patiënten een acute achteruitgang hadden van de nierfunctie, 1 patiënt had een meer geleidelijke achteruitgang in de nierfunctie en 2 patiënten hadden aanvankelijk een achteruitgang en later een stabilisatie van de nierfunctie. Twee patiënten ontwikkelden eindstadium

nierfalen met noodzaak tot dialyse, 3 patiënten ontwikkelden ernstig nierfalen en 1 patiënt overleed als gevolg van stamceltransplantatie nefropathie. Behandeling met een ACE-remmer (bloeddrukverlagend medicijn) stabiliseerde de nierfunctie bij slechts 1 van de 5 patiënten.

In **hoofdstuk 5** worden chronische nierziekten na een myeloablatieve stamceltransplantatie beschreven. Het bleek dat chronische nierziekten voorkwamen bij 20% van de patiënten na 5 jaar. Slechts 2 patiënten hadden dialyse nodig. Risicofactoren voor chronische nierziekten waren lage glomerulaire filtratiesnelheid (verminderde nierfunctie) ten tijde van de stamceltransplantatie, vrouwelijk geslacht en hogere leeftijd. Meer dan de helft van de patiënten die al een lichte nierfunctiestoornis hadden voor de stamceltransplantatie ontwikkelden chronische nierziekten. De patiënten die een hoge bloeddruk ontwikkelden na de stamceltransplantatie kregen vaker chronische nierziekten. De patiënten die acuut nierfalen hadden gehad, kregen niet vaker chronische nierziekten en we konden geen relatie vinden tussen cyclosporine gebruik en chronische nierziekten. Het syndroom stamceltransplantatie nefropathie was de oorzaak van chronische nierziekten bij slechts 6 patiënten, maar was de enige oorzaak van eindstadium nierfalen bij beide patiënten die dialyse nodig hadden.
Ongeveer 60% van de patiënten was in leven na 5 jaar. Er was geen verschil in overleving tussen de patiënten met en zonder chronische nierziekten.

In **hoofdstuk 6** worden chronische nierziekten na een niet-myeloablatieve stamceltransplantatie beschreven. Het bleek dat chronische nierziekten voorkwamen bij 22% van de patiënten na 4 jaar. Er waren geen patiënten die dialyse nodig hadden. Risicofactoren voor chronische nierziekten waren lage glomerulaire filtratie snelheid (verminderde nierfunctie) ten tijde van de stamceltransplantatie, vrouwelijk geslacht en hogere leeftijd. Ongeveer een kwart van de patiënten die al een lichte nierfunctiestoornis hadden voor de stamceltransplantatie ontwikkelden chronische nierziekten. De patiënten die acuut nierfalen hadden gehad, kregen niet vaker chronische nierziekten en we konden geen relatie vinden tussen cyclosporine gebruik en chronische nierziekten. Er waren geen gevallen van stamceltransplantatie nefropathie.
Na 4 jaar was 66% van de patiënten in leven. Er was geen verschil in overleving tussen de patiënten met en zonder chronische nierziekten.

Uit deze 3 studies kan geconcludeerd worden, dat chronische nierziekten vaak voorkomende complicaties zijn na een stamceltransplantatie. Het syndroom stamceltransplantatie nefropathie is zeldzaam en kan ontstaan als er een hoge dosering totale lichaamsbestraling wordt gegeven in het myeloablatieve behandelingschema. Het is

echter een belangrijk syndroom, omdat het de enige oorzaak van eindstadium nierfalen is dat vroeg na de stamceltransplantatie kan ontstaan.
Chronische nierziekten die niet veroorzaakt worden door stamceltransplantatie nefropathie komen vaker voor bij patiënten met al een lichte nierfunctiestoornis voor stamceltransplantatie. Vrouwen en oudere patiënten zijn meer gevoelig voor achteruitgang in de nierfunctie. Het mechanisme dat aan chronische nierziekten ten grondslag ligt is niet duidelijk, maar een combinatie van factoren (chemotherapie, totale lichaamsbestraling, nierschadelijke medicijnen en graft-versus-host disease) zouden chronische nierziekten kunnen veroorzaken bij de patiënten met een lichte nierfunctiestoornis voor stamceltransplantatie of bij de patiënten die om andere reden voor nierschade gevoelig zijn.
Chronische nierziekten hadden geen invloed op de overleving van de patiënten. De reden hiervoor kan zijn dat de patiënten nog te kort gevolgd waren om late complicaties van chronische nierziekten te ontwikkelen, zoals hart- en vaatziekten. Bovendien gaat de nierfunctie met de leeftijd achteruit en chronische nierziekten kunnen in de loop der jaren verergeren tot eindstadium nierfalen. Hopelijk zal behandeling volgens de richtlijnen, opgesteld door behandelaren van nierziekten, verslechtering van chronische nierziekten tot nierfalen kunnen afremmen.

In **hoofdstuk 7** wordt beschreven hoe het is gegaan met 15 patiënten met een milde nierfunctiestoornis voor een niet- myeloablatieve stamceltransplantatie. We vonden dat 33% van deze patiënten chronische nierziekten ontwikkelden na de stamceltransplantatie, bij de controle patiënten met een normale nierfunctie voor de stamceltransplantatie was dit 17%. Geen van de patiënten had dialyse nodig. Bovendien verbeterde de nierfunctie na de stamceltransplantatie in meer dan de helft van de patiënten met een nierfunctiestoornis voor de stamceltransplantatie. Er was geen verschil in het optreden van complicaties na de stamceltransplantatie tussen beide groepen patiënten. De dosering van cyclosporine, de duur van behandeling met cyclosporine en de bloedspiegels van cyclosporine waren gelijk voor de patiënten met een nierfunctiestoornis en de patiënten met een normale nierfunctie. Er was geen verschil in overleving tussen de patiënten met nierfunctiestoornis en de patiënten met een normale nierfunctie.

Uit deze laatste studie kunnen we concluderen, dat een niet-myeloablatieve stamceltransplantatie veilig kan worden aangeboden aan de patiënten met een milde nierfunctiestoornis. Cyclosporine kan in dezelfde dosering worden toegediend als aan de patiënten zonder een nierfunctiestoornis, zolang cyclosporine bloedspiegels en creatinine in de gaten worden gehouden en dosis aanpassingen worden

doorgevoerd als het nodig is. Voor de patiënten die wel chronische nierziekten ontwikkelen moet behandeling volgens richtlijnen, opgesteld door behandelaren van nierziekten, worden toegepast.

Dankwoord

Dankwoord

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Curriculum Vitae

Curriculum Vitae

Sabina Kersting werd op 6 april 1975 geboren in Zeist en groeide op in Driebergen. Vanaf de kleuterklas tot aan de 7e klas zat zij op de Vrije school in Driebergen, daarna ging zij naar de bovenbouw van de Vrije School in Zeist. In het dertiende jaar deed zij eindexamen VWO in 8 vakken, waaronder muziek. In 1994 werd zij ingeloot voor Geneeskunde in Maastricht. In het derde jaar van de opleiding studeerde zij 10 maanden in Zweden aan Karolinska Institutet in Stockholm. Daar nam zij deel aan de reguliere derdejaars vakken van de Zweedse artsenopleiding, waaronder 6 maanden deeltijd co-schappen Interne Geneeskunde.
Terug in Maastricht deed zij het vierde jaar van de studie en behaalde haar doctoraal. In 1999 begon zij aan haar co-schappen in Utrecht en ging zij samenwonen in Zeist. Na het afronden van de geneeskunde opleiding werd zij AGNIO interne Geneeskunde in het Diakonessenhuis Utrecht. In 2001 startte zij met de opleiding Interne Geneeskunde in het UMC Utrecht met als opleider Prof. Dr. D.W. Erkelens. In 2002 trouwde zij met S.J. Huisman en een jaar later verhuisden ze naar Utrecht waar in 2006 hun dochter werd geboren. Nog voor de start van haar aandachtsgebied hematologie begon zij onder leiding van Dr. L.F. Verdonck met het onderzoek naar nierfunctiestoornissen na stamceltransplantatie, dat geleid heeft tot dit proefschrift. Momenteel doet zij onderzoek naar immuunreconstitutie van gamma-delta T-cellen na allogene stamceltransplantatie in het kader van een onderzoeksjaar voor arts-assistenten van het Koningin Wilhelmina Fonds. Zij hoopt haar opleiding tot internist-hematoloog in maart 2009 af te ronden.