Bone Marrow Transplantation Nephropathy after an Intensified Conditioning Regimen with Radioimmunotherapy and Allogeneic Stem Cell Transplantation

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Intensification of the conditioning regimen with a radioactively labeled anti-CD66 antibody is feasible before allogeneic stem cell transplantation. The use of radioimmunotherapy may deliver a significant dose of radiation to the kidneys. We therefore studied the incidence and clinical picture of bone marrow transplantation (BMT) nephropathy in our patients receiving radioimmunotherapy before allogeneic stem cell transplantation. **Methods:** This study was a clinical trial of 114 consecutive patients who received conditioning with a radiolabeled anti-CD66 antibody—[188]Re ($n = 93$) or [90]Y ($n = 21$)—between 1998 and 2003. **Results:** Although BMT nephropathy has developed in none of the patients in the [^{90}Y]anti-CD66 group, 6 of 93 patients receiving [[188]Re]anti-CD66 presented with signs of BMT nephropathy at a median of 11.5 mo after stem cell transplantation. The absorbed renal dose was significantly lower in the ^{90}Y group (4 vs. 7 Gy, $P < 0.0001$). Of the patients receiving [[188]Re]anti-CD66 who are alive, BMT nephropathy developed in 19% (6/32). Five of 6 patients with BMT nephropathy received total-body irradiation. The patients presented with elevated serum creatinine, proteinuria, anemia, hypertension, and signs of microangiopathy. All 6 patients in whom BMT nephropathy has developed are alive at a median follow-up of 58 mo after stem cell transplantation, and 1 patient has entered a dialysis program. **Conclusion:** BMT nephropathy appears to be a significant problem after allogeneic stem cell transplantation with intensified conditioning using the [188]Re-labeled anti-CD66 applied in this study, particularly when combined with total-body irradiation.

Key Words: radioimmunotherapy; BMT nephropathy; [188]Re; [90]Y

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Renal dysfunction and renal failure are common complications of allogeneic bone marrow transplantation (BMT) and stem cell transplantation (SCT) (1–7). Patients undergoing allogeneic SCT have been shown to have a 50% decrease in mean baseline glomerular filtration rate at 6 mo (2). In 5%–15% of patients, acute renal failure develops after SCT, and chronic renal insufficiency will develop in 5%−20% of the long-term survivors (4,5). One of the most common causes of chronic renal dysfunction is a syndrome resembling radiation nephritis that has been called BMT nephropathy (or late-onset BMT nephropathy) (6,7). The syndrome is tightly linked to the use of total-body irradiation (TBI), and diagnosis is based on the appearance of azotemia, hypertension, and disproportionate anemia 6 mo or more after transplantation (6). Additional features include microangiopathy, hemolysis, proteinuria, and occasionally hyperkalemia (5). Kidney biopsy specimens from patients with BMT nephropathy are characterized by mesangiolysis, atrophy, and tubulointerstitial scarring (8,9). Severe cases have features of thrombotic thrombocytopenic purpura (TTP), and some overlap occurs between BMT nephropathy and the TTP/hemolytic uremic syndrome spectrum of diseases (10).

Since 1998, we have used radiolabeled monoclonal antibodies against CD66 as a way to intensify the conditioning regimen before allogeneic SCT (11–13). This approach permits the delivery of high doses of radiation to the marrow while sparing nontarget organs such as the liver or kidney. Nonetheless, we have seen cases of BMT nephropathy in the subgroup of patients receiving radioimmunotherapy. The aim of the current study was to assess the incidence and delineate the clinical features of BMT nephropathy in a larger cohort of patients with long-term

follow-up who received radioimmunotherapy before allogeneic SCT.

MATERIALS AND METHODS

Patients

Patients at a high risk of relapse after conventional SCT were included in this study and received radioimmunotherapy. Thus, we included primarily patients with acute myelogenous leukemia beyond the first complete remission, patients with acute myelogenous leukemia in the first complete remission if high-risk cytogenetic features were present or there was a poor response to primary-induction chemotherapy, patients with chronic myelogenous leukemia beyond the first chronic phase, patients with high-risk acute lymphoblastic leukemia, and patients with high-risk myelodysplastic syndrome (refractory anemia with excess blasts or refractory anemia with excess blasts in transformation) (Table 1). Patients were required to be in complete remission or partial remission, defined respectively as no blasts in the peripheral blood and 25% or fewer blasts in the marrow. We accepted human leukocyte antigen–identical or mismatched family members, a haploidentical sibling or parent, or matched unrelated volunteers as donors. Patients were required to be free of medical conditions excluding them from high-dose chemoradiotherapy and to have a favorable dosimetry. Between 1998 and 2003, a total of 7 patients did not receive radioimmunotherapy because of unfavorable dosimetry or disease progression before transplantation and were not included in the current study (low marrow dose [$n = 3$], higher kidney dose than marrow dose [$n = 2$], high myelon dose [$n = 1$] after previous radiotherapy, or progressive disease [$n = 1$]). More recently, we have used a reduced-intensity conditioning regimen combined with radioimmunotherapy (14). Favorable dosimetry was defined as a marrow or spleen dose higher than that of any other organ.

Over a period of 5 y (median follow-up, 44.6 mo), 114 patients underwent allogeneic SCT after intensified conditioning (Table 1). The population consisted of 70 male patients and 44 female patients; the median age was 47 y (range, 17−67 y). The diagnosis was acute myelogenous leukemia in 64 patients, acute lymphoblastic leukemia in 22, chronic myelogenous leukemia in 17, and myelodysplastic syndrome in 5 (Table 1). Study endpoints were the unfeasibility or toxicity of the procedure, the incidence of acute or chronic graft-versus-host disease, and the frequency of relapse and treatment-related mortality. The protocol for the study was approved by the Ethics Committee of Ulm University, and all patients and donors gave their written, informed consent.

Antibody Labeling

The antibody used for radioimmunotherapy was the anti-CD66 (a, b, c, e) monoclonal antibody (Scintimun granulocyte; Cis Bio International). This is a mouse IgG$_1$ antibody with a high affinity for the CD66 antigen (2×10^9 mol/L) (15). The development of human antimouse antibodies was not clinically relevant, and we could not detect human antimouse antibodies in the patients evaluated. ^{188}Re was obtained from a ^{188}W/^{188}Re radionuclide generator as a solution of sodium perrhenate in saline. The generator was supplied by the Oak Ridge National Laboratory. Full details of generator performance have been published elsewhere (16). The labeling procedure for the antibody has previously been described (17). For radiolabeling with ^{188}Re, a direct antibody-labeling approach was used. Disulphide bonds of

TABLE 1
Characteristics and Conditioning of Patients Receiving Radioimmunotherapy

Characteristic	^{188}Re ($n = 93$)	^{90}Y ($n = 21$)
Age (y)		
Median	46	49
Range	17–64	18–67
Sex		
Female	39	5
Male	54	16
Diagnosis		
Acute myelogenous leukemia/ myelodysplastic syndrome/ myeloproliferative syndrome	57	13
Acute lymphoblastic leukemia	17	5
Chronic myelogenous leukemia	14	3
Chronic lymphocytic leukemia/ prolymphocytic leukemia	5	0
Stem cell source		
Bone marrow	9	2
Peripheral blood	84	19
Donor		
Matched related	42	8
Matched unrelated	29	9
Mismatched related	3	0
Mismatched unrelated	7	2
Haploidentical	12	2
Conditioning		
TBI, cyclophosphamide	43	3
Busulfan, cyclophosphamide	26	9
TBI, cyclophosphamide, thiotepa	11	1
Fludarabine ± antithymocyte globulin	6	4
Fludarabine, melphalan, antithymocyte globulin	4	2
TBI, melphalan	1	0
Fludarabine, thiotepa, melphalan	1	0
TBI, cyclophosphamide, thiotepa	1	0
Cyclosporin immunosuppression	31	3

TBI = 12 Gy; cyclophosphamide = 2×60 mg/kg; thiotepa = 10 mg/kg; fludarabine = 5×30 mg/m^2; antithymocyte globulin = 4×5 mg/kg.

the proteins were reduced by mild reduction with Tris(2-carboxyethyl)phosphine. Afterward, the generated sulfhydryl groups were labeled with ^{188}Re. Quality control included high-pressure liquid chromatography with simultaneous monitoring of protein (ultraviolet absorption at a 280-nm wavelength) and radioactivity (NaI γ-detector) to characterize the labeled product, as well as instant thin-layer chromatography to determine the amount of colloids. The radiochemical purity of the ^{188}Re-labeled anti-CD66 was more than 94%. Colloidal ^{188}Re was less than 2%. The immunoreactivity of the reduced antibodies was 99.3%. High-performance liquid chromatography of blood serum demonstrated fewer than 15% radiolabeled low-molecular-weight antibody fragments and less than 2% ^{188}Re-perrhenate, indicating that the radioimmunoconjugate was metabolically stable in vivo (17).

The anti-CD66 antibody was labeled with ^{111}In or ^{90}Y in 2 steps. In a first step, the bifunctional chelator (2-parathiocyanotobenzyl-6-methyl-diethylenetriaminepentaacetic acid) was attached to the

antibody. In a second step, the radiometal was complexed via the chelator. Briefly, 10 mg of antibody were dissolved in 1 mL of *N*-(2-hydroxyethyl)piperazine-*N'*-(2-ethanesulfonic acid) (HEPES) buffer (0.05 mol/L, ph 7.9). Eighteen milligrams of *p*-isothiocyanatobenzyl-diethylenetriaminepentaacetic acid (mx-DTPA; Macrocyclics) were dissolved in HEPES buffer, adjusted to pH 7.9, added to the antibody solution (molar ratio, 1:500). The immunoreactivity was determined to be more than 90%. An aliquot of the labeled antibody was subjected to size-exclusion chromatography or high-performance liquid chromatography to evaluate the radiochemical purity. Subsequently, the antibody solution was sterilized by filtration (Millipore). The in vivo stability of the radioimmunoconjugate was evaluated by subjecting serum obtained after the antibody infusion to gel-exclusion chromatography. The average radiochemical purities of the ^{111}In- and ^{90}Y-labeled monoclonal antibodies determined by size-exclusion chromatography or high-performance liquid chromatography were 96% ± 3% and 95% ± 3%, respectively. After 24 and 48 h of incubation with serum at 37°C, 92% and 83%, respectively, of the activity were still bound to the antibody.

Dosimetry

The methodology used for dosimetry in our study has been published recently (*18*). In all patients receiving ^{188}Re, individual dosimetry was performed after intravenous infusion of 500−800 MBq of [^{188}Re]anti-CD66 (1 mg of anti-CD66). Biodistribution of radioimmunoconjugates was measured with whole-body imaging by means of a γ-camera (Whole Body Imager; Siemens) in anterior and posterior projections at 1.5, 3, 20, and 26 h and 2 d after injection. Excretion of radioactivity in the urine was quantitatively determined until 2 d after injection. The percentage injected dose in organs was determined by the geometric mean of counting rates sampled from anterior and posterior regions of interest by γ-camera images of respective tissue or organs. Bone marrow activity was determined by a rectangular region of interest over the second to fourth vertebral bodies of the lumbar spine. To scale this activity to total bone marrow, 4 rectangular regions of interest—1 each over the spine, the ribs, the pelvis, and the femurs—were drawn to estimate the corresponding multiplication factor (*18*). Representative dosimetry images are shown in Figure 1. After calibration and subtraction of radioactivity excreted with urine, whole-body radioactivity measured by γ-camera was normalized to the injected dose. Radioactivity in the remainder of the body was calculated by subtracting the sum of organ radioactivity from the whole-body radioactivity. Decay-corrected radioactivity of organs with significant radioactivity retention (bone marrow, liver, spleen, and kidneys) and the remainder of the body were fitted with up to 3 coupled exponential functions with up to 4 parameters (*19*). Organ residence times were determined and absorbed dose calculated using MIRDOSE3 software (*20*).

For patients who were treated with the ^{90}Y-labeled antibody, dosimetry was performed with the surrogate tracer ^{111}In because ^{90}Y is a pure β-emitter. All patients received an infusion of 1 mg of anti-CD66 antibody labeled with 100 MBq of ^{111}In. The biodistribution of radioimmunoconjugates was measured with whole-body imaging by means of a γ-camera (Whole Body Imager) in anterior and posterior projections at 2 and 4 h and 1, 2, 3, and 4 or 6 d after injection. Excretion of radioactivity in the urine was quantitatively determined until 6 d after injection. The dose calculation was performed as already described.
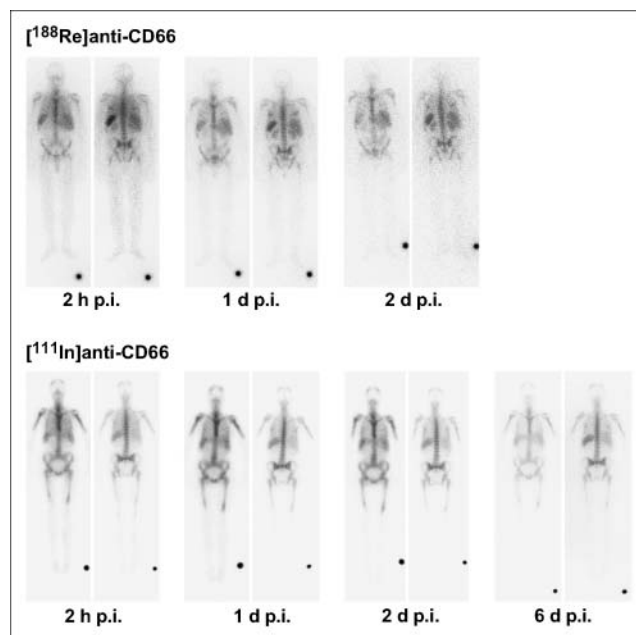
FIGURE 1. Representative planar γ-camera images of patients receiving ^{188}Re and ^{111}In (left, mirrored anterior; right, posterior). p.i. = after injection.

Radioimmunotherapy

Patients with a favorable biodistribution were treated. Our intention was to give each patient the highest tolerable dose. The dose injected was determined by the results of the biodistribution studies, the activity of the generator, and the type of conditioning. For patients receiving additional TBI with 12 Gy, the limiting doses for the bone marrow and liver were derived from the studies of Matthews et al. and set at 25 Gy and 7–10 Gy, respectively (*21,22*). The upper limit for the kidney was defined as 12 Gy on the basis of published studies on the radiation tolerance of the kidneys (*22,23*). For patients not receiving TBI, the dose limits were 35 Gy for the marrow, 19–24 Gy for the liver, and 20 Gy for the kidneys (*24*). The therapeutic antibody was given intravenously over a period of 10 min in 1 or 2 fractions of 1 or 2 mg of labeled antibody 24–48 h after the completion of dosimetry and on day 14 before the transplantation to ensure elimination of the nuclide. Dose fractionation had no influence on the biodistribution of the antibody (*18*). To prevent ^{188}Re uptake into the thyroid gland and gastric mucosa, we treated patients receiving ^{188}Re with 3 × 480 mg of perchlorate (Irenat; Bayer) beginning 24 h before dosimetry and continuing for 1 wk after the last antibody infusion. In the presence of perchlorate treatment, we did not see significant thyroid uptake of ^{188}Re. Radioimmunotherapy was performed in radiation isolation rooms, and patients usually remained there for 48 h as required by German radioprotection regulations.

Conditioning

All patients were given additional conditioning therapy after radioimmunotherapy. Various protocols were used (Table 1). The majority of patients with matched family donors and matched unrelated donors were treated with either TBI (12 Gy) plus cyclophosphamide (120 mg/kg) ($n = 46$) or intravenous busulfan (12.8 mg/kg) plus cyclophosphamide (120 mg/kg) ($n = 37$). Most patients with haploidentical family donors ($n = 14$) were

conditioned with TBI (12 Gy) plus thiotepa (10 mg/kg) plus cyclophosphamide (120 mg/kg) ($n = 12$). In all patients receiving TBI, renal shielding was used to reduce the radiation exposure of the kidneys from TBI to 6 Gy (25). In patients with mismatched family donors or receiving a graft from a matched unrelated donor, antithymocyte globulin (5 mg/kg; Fresenius) from day −4 to day −1 was added to prevent graft rejection ($n = 54$).

Donors and Grafts

One hundred three patients received peripheral blood stem cell grafts mobilized by granulocyte colony-stimulating factor; bone marrow was the source of stem cells in 11 cases. Peripheral blood stem cell grafts were obtained by treating donors with granulocyte colony-stimulating factor (2×6 μg/kg/d) for 4–6 d. Between days 4 and 6 of the granulocyte colony-stimulating factor treatment, 1–3 leukaphereses were performed using the Spectra (Cobe) cell separator. Bone marrow was harvested by multiple aspirations under general anesthesia. The donors were human leukocyte antigen–identical siblings in 50 cases, matched unrelated donors in 38 cases, a mismatched family donor in 3 cases, a mismatched unrelated donor in 9 cases, and a haploidentical family member in 14 cases (Table 1).

Graft-Versus-Host Disease Prophylaxis

One hundred six of the 114 allogeneic stem cell grafts were T cell depleted. Two methods of T-cell depletion were used, depending on the risk of graft-versus-host disease. In patients with human leukocyte antigen–compatible family donors, 39 grafts were T cell depleted by adding the humanized anti-CD52 monoclonal antibody alemtuzumab (Campath 1 H; Genzyme) to the leukaphereses (26). Depending on the nucleated cell count, 10, 20, or 30 mg of Campath 1 H were added to each peripheral blood stem cell graft or bone marrow graft, and the antibody and cell suspension were gently mixed for 30 min at room temperature. In 64 patients receiving a peripheral blood stem cell graft, T-cell depletion was performed by CD34$^+$ selection using the immunomagnetic CliniMACS device (Miltenyi Biotec) (27). The target doses were less than 1×10^5/kg for T cells and less than 5×10^4/kg for CD3$^+$ cells. Bone marrow from matched unrelated donors was T-cell depleted using the Campath 1 H in-the-bag approach in 3 cases (28). T-cell depletion was the sole means of prophylaxis for graft-versus-host disease in 50 patients. Cyclosporine (target trough blood level, 2×2.5 mg/kg [200−250 μg/L]) was given to 34 patients.

Supportive Care

Patients were treated in single rooms. Irradiated erythrocytes and platelets were transfused if the hemoglobin level dropped below 80 g/L (8 g/dL) or the platelet count dropped below 20×10^9/L (20,000/μL). Cytomegalovirus-seronegative blood donors were used if both stem cell donor and recipient were cytomegalovirus seronegative. All patients were given prophylactic ofloxacin, fluconazole, acyclovir, and cotrimoxazole (trimethoprim, 160 mg; sulfamethoxazole, 800 mg 3 times per week). Cytomegalovirus-seropositive patients were treated prophylactically. Preemptive therapy with ganciclovir, 2×5 mg/kg intravenously, or foscarnet, 3×60 mg/kg, was instituted if the cytomegalovirus antigenemia test showed positive findings. Prophylaxis with acyclovir, fluconazole, and cotrimoxazole was maintained until patients had achieved a CD4$^+$ T-cell level of more than 0.20×10^9/L (200/μL).

BMT Nephropathy

Late-onset BMT nephropathy was defined according to the Lawton criteria: azotemia, hypertension, and disproportionate anemia occurring at least 6 mo after transplantation (6,7). For the diagnosis to be confirmed, these signs had to be present in the absence of nephrotoxic medication, sepsis, antifungal therapy, prior renal irradiation, cyclosporine toxicity, or significant graft-versus-host disease. Nephrotoxic medication during the months before development of the syndrome was reviewed (6). Because the syndrome can be diagnosed on clinical grounds, a renal biopsy was not considered necessary to make the diagnosis (5,29,30). Cases of TTP were not a focus of the current analysis. TTP was diagnosed according to published criteria when the following were present: hemolytic anemia, with peripheral blood smear schistocytes in the absence of disseminated intravascular coagulation; thrombocytopenia; elevated lactate dehydrogenase; new-onset renal insufficiency; and new-onset neurologic symptoms. At variance with BMT nephropathy, a diagnosis of thrombocytopenic purpura required that the hematologic component be clinically predominant (severe thrombocytopenia and microangiopathy) and that the onset occur within the first 120 d.

Statistical Analysis

The median follow-up for survival was calculated according to the method of Korn (31). Competing risk analysis was performed using the k-sample tests for comparing the cumulative incidence of a competing risk (32), and kidney dosimetry data were compared using the 2-tailed t test.

RESULTS

Over a period of 5 y (April 1998–May 2003), we treated 114 patients (minimum follow-up, 12 mo) with high-risk leukemia with radioimmunotherapy before allogeneic SCT (Table 1). In 6 of these patients (5%), BMT nephropathy developed, as defined by the Lawton criteria (6,7), a median of 11.5 mo after transplantation (6−19 mo). At the diagnosis of BMT nephropathy, none of the patients were receiving nephrotoxic drugs (e.g., cyclosporine, FK506, or amphotericin B). A kidney biopsy was performed on 1 patient and showed altered capillary loops without microthrombi but with wide basal membranes, an atrophic tubular system (60%−70%), and a widened interstitium. Electron microscopic findings were characterized by unregularly widened capillary membranes with subendothelial edema. The characteristics of the patients with BMT nephropathy are shown in Table 2. The patients presented with hypertension ($n = 5$), anemia ($n = 6$), signs of microangiopathy ($n = 4$), proteinuria of varying degree ($n = 6$) (234−3,144 mg/L), and thrombocytopenia ($n = 6$) (Table 2). Before transplantation, the mean creatinine value was 79 μmol/L (SE, 5) in the ^{90}Y group and 80 μmol/L (SE, 3) in the ^{188}Re group. Six months after transplantation, the respective creatinine levels increased to 105 μmol/L (SE, 14) and 102 μmol/L (SE, 12), which was a statistically significant increase (t test, $P = 0.04$ [^{90}Y] and $P = 0.0003$ [^{188}Re]). At diagnosis of BMT nephropathy, the creatinine level had increased to a median of 166 μmol/L (123−204 μmol/L) (Fig. 2). At the last follow-up, the patients had

TABLE 2
Characteristics of Patients with BMT Nephropathy at Diagnosis

Characteristic	Unique patient number					
	664	717	737	788	806	876
Age (y)	33	47	25	33	32	45
Sex	F	M	F	F	M	F
Diagnosis	Acute myelogenous leukemia	Myelodysplastic syndrome	Chronic myelogenous leukemia	Acute myelogenous leukemia	Chronic myelogenous leukemia	Acute myelogenous leukemia
Donor	Haploidentical sibling	Sibling	Haploidentical sibling	Matched family donor	1-mismatch matched family donor	Matched family donor
Stem cell source	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood	Peripheral blood	Bone marrow
Conditioning	TBI, cyclophosphamide, thiotepa	TBI, cyclophosphamide	TBI, cyclophosphamide, thiotepa	TBI, cyclophosphamide	TBI, cyclophosphamide	Busulfan, cyclophosphamide
Radioimmunotherapy source	[188]Re	[188]Re	[188]Re	[188]Re	[188]Re	[188]Re
Graft-vs.-host disease	Acute, grade 1	None	None	Acute, grade 2	Chronic	None
Cyclosporine use	None	None	None	None	None	Yes*
Bone marrow dose (Gy)	16	11	10	20	18	21
Kidney dose (Gy)	5	8	2	9	6	12
Hypertension	+	+	+	+	+	−
Hemoglobin (g/dL)	10.2	10.2	8.7	9	6.8	6.2
Lactate dehydrogenase (U/L) (normal, <250)	Not done	285	519	157	329	324
Schistocytes	Not done	+	+	−	+	+
Erythropoietin level (U/L) (normal, 3.3–16)	Not done	Not done	32.2	1.7	110.4	32.6
Hematuria	−	+	+	+++	+	+++
Proteinuria (mg/L)	+	1,024	3,144	554	234	1,130
Platelet count	106	96	61	92	106	73

*Discontinued 5 mo before onset of BMT nephropathy.
TBI = 12 Gy; cyclophosphamide = 120 mg/kg; busulfan = 12.8 mg/kg.
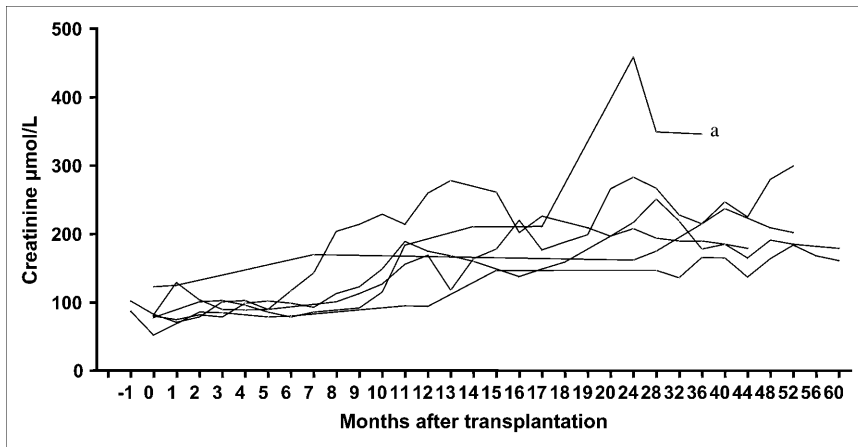
FIGURE 2. Creatinine values at different times for patients with BMT nephropathy. a = initiation of hemodialysis.

a median creatinine value of 210 µmol/L (163−349 µmol/L). In 3 of 6 patients, the creatinine value peaked before declining again (median maximum, 244 µmol/L; range, 184−459 µmol/L). Three patients showed steadily increasing creatinine values, and 1 patient entered a chronic dialysis program (Fig. 2).

Thus far, BMT nephropathy has developed only in patients receiving [188]Re (Fig. 3A). In the [188]Re subgroup, the incidence of BMT nephropathy was 6% (6/93). Of the patients who are alive, BMT nephropathy has developed in 19% (6/32). In the [188]Re group, 37 patients experienced relapse at a median of 5.4 mo after the transplantation (40%). The cumulative incidence of death was 66%, with most patients dying from causes other than relapse (40%)

or from relapse (26%). Since December 2001, patients have received ^{90}Y-labeled antibody instead of [188]Re-labeled antibody. No patient receiving ^{90}Y has been diagnosed with BMT nephropathy (Fig. 3A). Because of the shorter follow-up (19.2- vs. 48.2-mo median follow-up) and fewer patients, this difference is not significant in a competitive risk analysis (Fig. 3A). Nine of 21 patients receiving ^{90}Y have died (5 from causes other than relapse and 4 from relapse). Six patients have experienced relapse (29%), at a median of 5.7 mo after transplantation. The mean kidney dose for patients receiving ^{90}Y was 4 Gy ($\pm$0.5), compared with a mean kidney dose of 7 Gy ($\pm$0.3) for patients receiving [188]Re (t test, $P < 0.0001$) (Fig. 4). The mean bone marrow dose for patients receiving ^{90}Y was 20 Gy, compared with 14 Gy for patients receiving [188]Re. The lungs received very little additional radiation by radioimmunotherapy (0.6 and 0.8 Gy for ^{90}Y and [188]Re, respectively).

Within the group of patients receiving TBI ($n = 60$), BMT nephropathy developed in 5 (8%). Only 1 patient who did not receive TBI had BMT nephropathy (2%) ($P = 0.12$ in competing risk analysis) (Fig. 3B). When only the
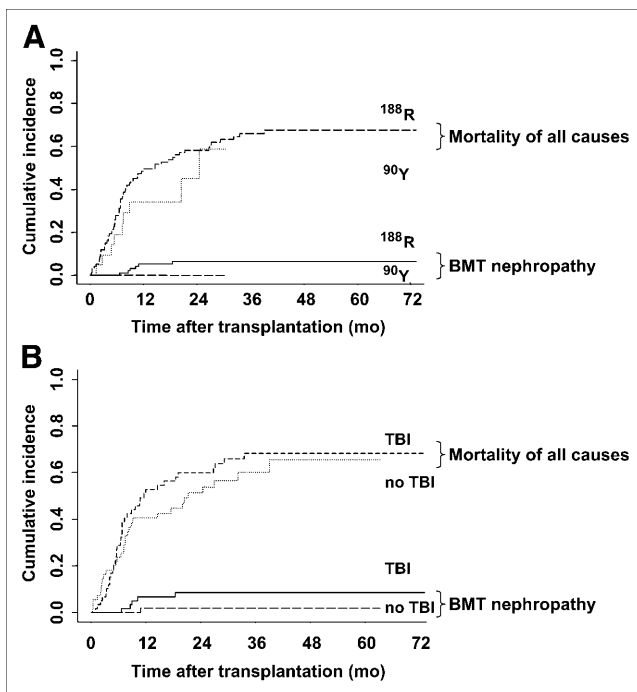
FIGURE 3. (A) Competitive risk analysis for patients receiving [188]Re and [90]Y ($P = 0.27$). (B) Competitive risk analysis for patients with and without TBI ($P = 0.12$).
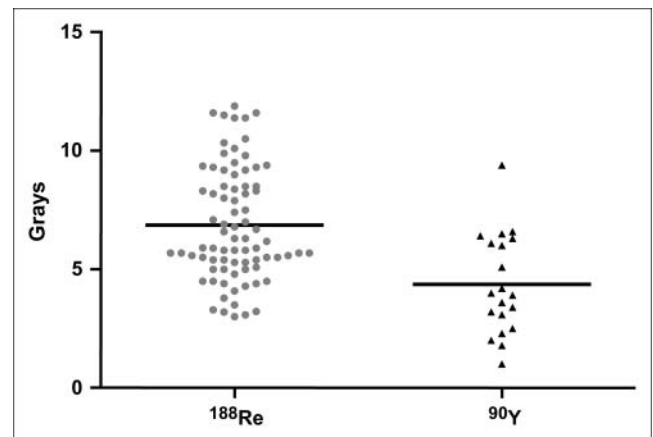
FIGURE 4. Renal dose as calculated by dosimetry for patients receiving [188]Re vs. [90]Y (6.9 $\pm$ 0.3 Gy vs. 4.4 $\pm$ 0.5 Gy; t test, $P < 0.0001$).

surviving patients are considered, the difference approaches statistical significance (log rank test, $P = 0.053$). The kidney radiation dose delivered by radioimmunotherapy did not differ between the group treated with TBI and the group treated without TBI (median, 6.5 vs. 6.2 Gy). The mean kidney dose delivered by radioimmunotherapy in patients with BMT nephropathy was 7 Gy (± 1.2 Gy), compared with 6 Gy (± 0.3 Gy) in the patients without BMT nephropathy. One patient received a very low radiation dose to the kidney by radioimmunotherapy (2.3 Gy), yet BMT nephropathy still developed.

All patients were treated with antihypertensive medication and received angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. At the last follow-up, 5 of 6 patients were still being treated with ACE inhibitors or angiotensin receptor blockers. While on antihypertensive medication and ACE inhibitors or angiotensin receptor blockers, 3 of 6 patients (including the patient who underwent renal biopsy) experienced improved renal function after an initial decline (Fig. 2). Five patients received erythropoietin, and at the last follow-up 4 of these patients were still receiving erythropoietin. All 6 patients in whom BMT nephropathy developed are alive, at a median follow-up of 58 mo after SCT.

DISCUSSION

Renal failure and renal dysfunction are common sequelae of allogeneic SCT. The incidence of BMT nephropathy has not previously been studied in a large cohort of patients receiving radioimmunotherapy before allogeneic SCT. The incidence of BMT nephropathy in the current study was 5%. This incidence is in line with the experience from standard conditioning regimens including TBI: BMT nephropathy has been shown to occur in 0.8%−9.5% of adults undergoing conventional SCT, and the incidence in children may be even higher (5). Nonetheless, compared with patients at our center who received conventional conditioning, patients who additionally received radioimmunotherapy appeared to have an increased risk of nephrotoxicity (24). BMT nephropathy is a considerable problem in the patient population described. Because the mortality due to relapse and toxicity was high, as is expected for a high-risk population (advanced leukemia, old age, unrelated and mismatched donors), the incidence of BMT nephropathy in the group of alive patients receiving [188]Re-labeled anti-CD66 antibody was 19%.

The presenting symptoms of BMT nephropathy in the current study were similar to those previously reported for the syndrome (6,29,30). However, because of the low number of renal biopsies performed (1/6), we cannot exclude that atypical or mild BMT nephropathy occurred after radioimmunotherapy in some patients but remained undetected because we adhered to the established criteria for diagnosis. However, in other cases in which a renal biopsy was performed, an alternative diagnosis was found (e.g., interstitial nephritis or viral nephritis) (33). No cases of typical BMT nephropathy were found only on pathologic examination.

Three courses of BMT nephropathy have been described: a rapidly progressing form, a slowly progressing form, and a form characterized by stable renal function after an initial decline. In the current study, half the patients showed a slow but continuous rise in creatinine values, whereas the other half showed stable creatinine values over time. In fact, while on antihypertensive drugs, including ACE inhibitors or angiotensin receptor blockers, 3 patients (including the patient in whom BMT nephropathy was proven by biopsy) experienced improved renal function over time. Although most patients have only a moderate elevation of creatinine values even with long follow-up, 1 of our patients entered a chronic dialysis program.

The appearance of BMT nephropathy has been tightly linked to TBI, and the incidence increases with increasing TBI dose (5,34). Renal shielding has been shown to decrease the incidence of BMT nephropathy: The partial renal shielding used by Lawton et al. decreased the radiation exposure of the kidney from 14 to 12 Gy and led to a decrease in the incidence of BMT nephropathy from 26% to 6% (35). The renal shielding that we used reduced the radiation exposure by TBI from 12 to 6 Gy (24). Nonetheless, the incidence of BMT nephropathy in patients with TBI was 8% (vs. 2% without TBI), and 5 of the 6 patients in whom BMT nephropathy developed received TBI. This difference approached statistical significance in a competing risk analysis (Fig. 3B). In 3 of these patients, radiation delivered to the kidney by radioimmunotherapy was no more than 6 Gy. However, with radioimmunoconjugates the clear dose–toxicity relationship may not be derived by merely adding up the radiation doses from TBI and radioimmunotherapy. In addition, dosimetry—as currently practiced—does not take regional dose heterogeneity into account. The dose to the critical renal cortex may be underestimated. Methods taking these considerations into account, including PET dosimetry and dose calculations based on recently published calculations, may prevent renal toxicity (36). Other factors, such as the stability of the radiochemical–antibody compound, the kinetics of the exposure, and differences in dose rate between radioimmunotherapy and external-beam radiation, may contribute to development of the syndrome. The stability of the radionuclide–antibody complex may be a particular problem with [188]Re, which has been shown to dissociate from the antibody (17). Over time, the percentage of the administered activity increases in the urine, relative to other organs (2 h, 2%; 48 h, 36%) (17). This difference is explained by increased excretion of [188]Re-perrhenate over time. Because [188]Re-perrhenate is rapidly excreted through the kidneys, radiolabeled low-molecular-weight antibody fragments, which have been shown to be present by high-performance liquid chromatography, may have contributed to the renal toxicity (12,17,18). An alternative labeling procedure for [188]Re may increase stability. The instability of the [188]Re–antibody

complex was one of the reasons for switching to ^{90}Y. Since switching the radionuclide from ^{188}Re to ^{90}Y, we have not seen additional cases of BMT nephropathy. Because of the fewer patients and shorter follow-up, this difference is not significant and thus must be considered with caution. However, these results would be encouraging even if the conditioning regimen in the ^{90}Y and ^{188}Re groups were not identical with regard to the fraction of patients receiving TBI and reduced-intensity conditioning. The results must be confirmed with longer follow-up and more patients in the ^{90}Y group. Currently, it is not clear if the trend toward a lower incidence may be due to the decreased radiation dose to the kidney in the ^{90}Y-treated group (4 vs. 7 Gy, $P <$ 0.0001), the increased stability of the radioimmunoconjugates, or other unknown reasons. ^{90}Y has been shown to cause renal failure when tagged to a somatostatin receptor ligand (37). Because the propensity to cause renal failure depends largely on the intrarenal handling of peptides and antibodies, this difference might be explained. In fact, renal toxicity has not been reported after the application of a ^{90}Y-labeled anti-CD20 antibody in patients with lymphoma (38).

A number of alternative radioisotope compounds have been used in the setting of allogeneic SCT: A [^{131}I]anti-CD45 antibody (BC8) was used in a group of 37 patients with advanced leukemia and myelodysplasia (20). The absorbed kidney dose was 22.2 cGy/MBq of ^{131}I administered. Chronic renal impairment was not reported. A group from New York has published a phase I study using [^{131}I]anti-CD33 antibodies as part of the conditioning regimen (39). They treated 31 patients with advanced acute myelogenous leukemia and chronic myelogenous leukemia. Toxicity was mainly hepatic, and chronic renal impairment was not mentioned, but because of high mortality the median follow-up was only 4.9 mo (39). The group has recently started to use an ^{90}Y-labeled anti-CD33 antibody (40). Taken together, these studies suggest that renal toxicity may be more likely to occur when ^{188}Re with the current labeling approach is used. However, in the trials from other centers, BMT nephropathy may have not been seen simply because of the low overall number of patients (total of 77 patients in all trials combined) and high early mortality (20,39,41). With increasing numbers of patients treated with radioimmunotherapy before allogeneic SCT and more centers treating patients who received this particular compound (e.g., in Germany, centers in Frankfurt, Hannover, Dresden, and Ulm), more data on the problem of renal impairment are likely to emerge.

A study by Cohen et al. has shown a poor prognosis for patients in whom BMT nephropathy develops (29). In our study, all patients with BMT nephropathy are alive, suggesting that overall prognosis may not be altered by the occurrence of BMT nephropathy.

CONCLUSION

When using the directly labeled [^{188}Re]anti-CD66 antibody before allogeneic SCT, one must take into consideration chronic renal impairment, especially when radioimmunotherapy is combined with TBI. Measures to prevent the development of BMT nephropathy may include early use of ACE inhibitors, or angiotensin receptor blockers, or forced diuresis after the application of the antibody to decrease tubular exposure if the radiometal–antibody complex dissociates. Alternative labeling methods resulting in a more stable radiometal–antibody complex may help to decrease renal toxicity when using ^{188}Re.

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