Long-Term Renal Toxicity in Children Following Fractionated Total-Body Irradiation (TBI) Before Allogeneic Stem Cell Transplantation (SCT)

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Purpose: To retrospectively assess the incidence and time course of renal dysfunction in children (≤ 16 years) following total-body irradiation (TBI) before allogeneic stem cell transplantation (SCT).
Patients and Methods: Between 1986 and 2003, 92 children (median age, 11 years; range, 3–16 years) underwent TBI before allogeneic SCT. 43 of them had a minimum follow-up of 12 months (median, 51 months; range, 12–186 months) and were included into this analysis. Conditioning regimen included chemotherapy and fractionated TBI with 12 Gy (n = 26) or 11.1 Gy (n = 17). In one patient, renal dose was limited to 10 Gy by customized renal shielding due to known nephropathy prior to SCT. Renal dysfunction was defined as an increase of serum creatinine > 1.25 times the upper limit of age-dependent normal.
Results: Twelve children (28%) experienced an episode of renal dysfunction after a median of 2 months (range, 1–10 months) following SCT. In all but one patient renal dysfunction was transient and resolved after a median of 8 months (range, 3–16 months). One single patient developed persistent renal dysfunction with onset at 10 months after SCT. None of these patients required dialysis. The actuarial 3-year freedom from persistent renal toxicity for children surviving > 12 months after SCT was 97.3%.
Conclusion: The incidence of persistent renal dysfunction after fractionated TBI with total doses ≤ 12 Gy was very low in this analysis.

Key Words: Stem cell transplantation · Total-body irradiation · Long-term renal toxicity

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Renale Spättoxizität im Kindesalter nach fraktionierter Ganzkörperbestrahlung (TBI) vor allogener Stammzelltransplantation (SCT)

Ziel: In einer retrospektiven Analyse wurden die Inzidenz und der zeitliche Verlauf der renalen Spättoxizität bei Kindern (≤ 16 Jahre) nach Ganzkörperbestrahlung (TBI) vor allogener Stammzelltransplantation (SCT) untersucht.
Patienten und Methodik: Von 1986 bis 2003 erhielten 92 Kinder (medianes Alter 11 Jahre; Streubreite 3–16 Jahre) eine fraktionierte TBI vor allogener SCT. 43 Patienten wiesen eine Nachbeobachtungszeit von mindestens 12 Monaten auf (median 51 Monate; Streubreite 12–186 Monate) und gingen in diese Analyse ein. Die Konditionierung bestand aus einer Chemotherapie und einer fraktionierten TBI mit 12 Gy (n = 26) bzw. 11,1 Gy (n = 17). Bei einem Patienten wurde aufgrund einer vorbestehenden Nephropathie die Nierendosis durch individuelle Ausblockung auf 10 Gy begrenzt. Als renale Dysfunktion wurde ein Anstieg des Serumkreatinins über das 1,25fache des jeweils altersabhängigen oberen Grenzwerts nach SCT definiert.
Ergebnisse: Zwölf Kinder (28%) entwickelten eine renale Dysfunktion median 2 Monate nach SCT (Streubreite 1–10 Monate). Bei elf dieser Patienten war die renale Dysfunktion temporär mit Normalisierung nach median 8 Monaten (Streubreite 3–16 Monate). Nur bei einem Kind lag eine persistierende renale Dysfunktion vor, die 10 Monate nach SCT auftrat. Keines dieser Kinder wurde dialysepflichtig. Die aktuarische 3-Jahres-Freiheit von persistierenden renalen Funktionseinschränkungen bei Kindern mit einem Nachbeobachtungszeitraum von mindestens 12 Monaten nach SCT betrug 97,3%.
Schlussfolgerung: Die Inzidenz einer persistierenden renalen Dysfunktion nach fraktionierter TBI mit einer Gesamtdosis ≤ 12 Gy war in dieser Analyse sehr niedrig.

Schlüsselwörter: Stammzelltransplantation · Ganzkörperbestrahlung · Renale Dysfunktion

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Introduction

In patients with various malignant hematologic diseases, conditioning chemotherapy combined with total-body irradiation (TBI) followed by allogeneic stem cell transplantation (SCT) is a treatment approach with high curative potential [1, 15]. Due to the comparatively high radiosensitivity TBI is a commonly accepted treatment option in leukemia and malignant lymphoma before SCT [10, 16, 24, 28].

With longer follow-up, long-term side effects including chronic graft-versus-host disease (GVHD) may emerge, e.g., pulmonary and renal toxicities [8, 14, 18, 21, 27]. In children, lower organ-specific radiation tolerance doses have to be considered, although systematic reports on dose-dependent late effects in children are still missing up to now [3, 4]. So far, only limited data are available on long-term renal toxicity in children following TBI.

We here report our single-center experience regarding long-term renal side effects in children treated with TBI before SCT during a time period of 17 years and a minimum follow-up of 12 months.

Table 1. Treatment parameters in 43 children receiving fractionated total-body irradiation. AP/PA: anteroposterior/posteroanterior.

Tabelle 1. Bestrahlungsparameter der 43 Kinder mit fraktionierter Ganzkörperbestrahlung. AP/PA: anteroposterior/posteroanterior.

			Patients (n)
Total dose (Gy)			
11.1 (cobalt-60)			17
12.0 (linac-based)			26
Dose rate (Gy/min)			
Beams arrangements	Lateral	AP/PA	
Cobalt-60	0.05	0.55	17
Linac	0.15–0.25	0.75	26
Number of fractions/single dose (Gy)/fractions per day			
4/3/1			4
6/2/2			14
7–8/1.5–1.8/2			25

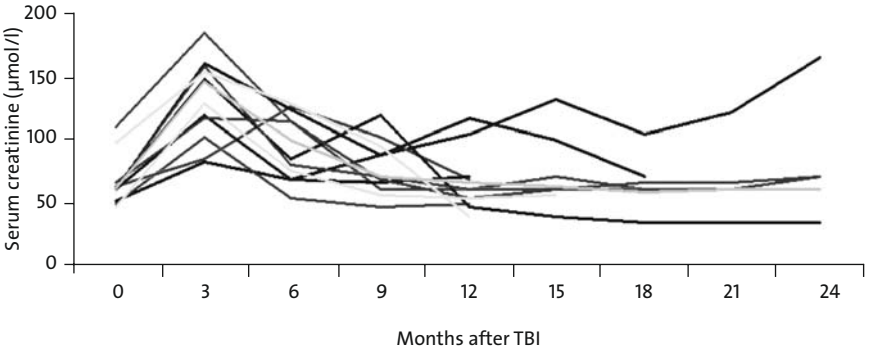


Figure 1. Individual serum creatinine values as a function of time in twelve children developing renal dysfunction after fractionated TBI.

Abbildung 1. Zeitlicher Verlauf der Serumkreatininwerte der zwölf Kinder mit renaler Dysfunktion nach fraktionierter TBI.

Patients and Methods

Between 01/1986 and 08/2003, 92 consecutive children (defined as patients ≤ 16 years at the time of SCT) were treated with TBI as part of their conditioning regimen before SCT at our department. Median age was 11 years (range, 3–16 years). Inclusion criteria for this long-term analysis were allogeneic SCT and a follow-up of at least 12 months. 46 (50%) children died within the first 12 months after SCT, while three children were lost to follow-up. The remaining 43 children fulfilled the inclusion criteria with a median follow-up of 51 months (range, 12–186 months).

The majority of children (n = 36, 84%) had acute lymphoblastic leukemia (ALL). The chemotherapy conditioning regimen consisted of etoposide alone (n = 31) or combined with cyclophosphamide (n = 6) or thiotepa (n = 6). 20 children were treated in first remission and 23 children in second remission. 27 children (62.5%) developed acute GVHD and nine children (20.9%) had chronic GVHD.

Total dose of fractionated TBI was 11.1 Gy using a cobalt-60 unit until 1993 and 12 Gy using a linac since 1994. Single doses ranged between 1.5 and 2.0 Gy with two daily fractions given on 3–4 consecutive days in the majority of patients (91%). TBI was performed using anteroposterior/posteroanterior and lateral portals at a ratio of 1/3 and 2/3, respectively. Details of TBI are given in Table 1. Lung dose was limited to 9 Gy using customized lung shielding. In one child, the renal dose was limited to 10 Gy by individual shielding due to known methotrexate-induced nephropathy prior to SCT.

For evaluation of renal function during follow-up, serum creatinine was chosen because this parameter could be obtained easily and consistently in all patients at different time points. Renal dysfunction was defined as an increase of serum creatinine > 1.25 times the upper limit of age-dependent normal. Data about creatinine clearance, proteinuria and hypertension were included into this evaluation if available in the patients records.

Statistical Analysis

All statistical analyses were performed using the software package SPSS, version 11.5. Overall and disease-free survival as well as survival without renal dysfunction were estimated using the Kaplan-Meier method. The following categorical variables were analyzed univariately using the log-rank test and multivariately using stepwise Cox proportional hazard analysis: gender, remission status at SCT (1st CR vs. > 1st

CR), diagnosis (ALL vs. non-ALL), chemotherapy regimen (cyclophosphamide vs. non-cyclophosphamide), GVHD (yes vs. no), total dose of TBI (11.1 Gy vs. 12 Gy), single dose of TBI (< 2.0 Gy vs. ≥ 2.0 Gy), and relapse after SCT (yes vs. no). The t-test was applied to correlate cumulative application days of potentially nephrotoxic drugs like cyclosporine A, acyclovir, aminoglycosides or vancomycin with occurrence of renal dysfunction.

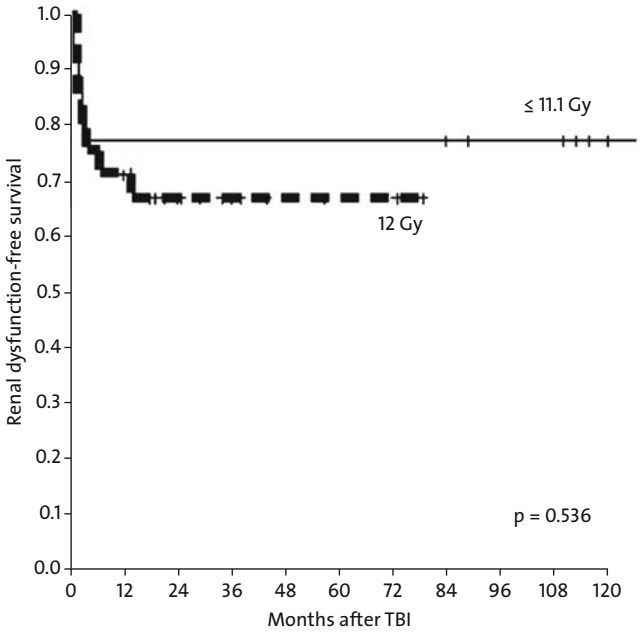
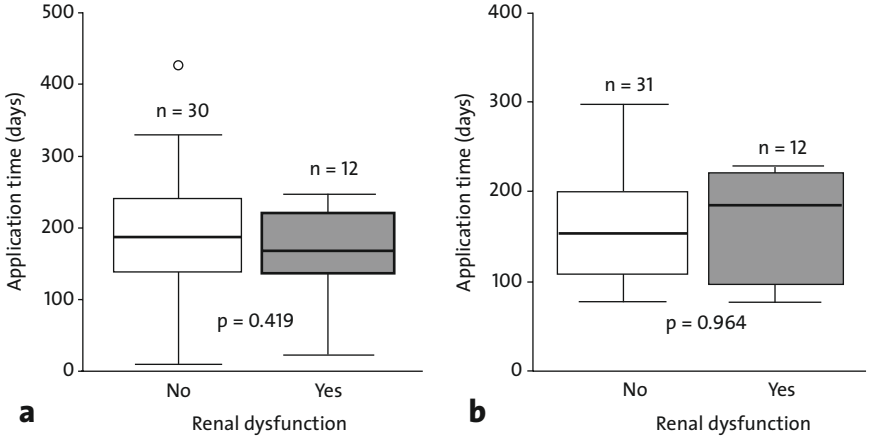


Figure 2. Actuarial renal dysfunction-free survival after fractionated TBI with doses ≤ 11.1 Gy versus 12 Gy (Kaplan-Meier, log-rank test, p = 0.536).

Abbildung 2. Überleben ohne Auftreten einer renalen Dysfunktion nach fraktionierter TBI mit ≤ 11,1 Gy versus 12 Gy (Kaplan-Meier, Log-Rank-Test, p = 0,536).



Figures 3a and 3b. Cumulative application days of a) cyclosporine A and b) acyclovir in early posttransplant period in children with (gray) and without (white) development of renal dysfunction. Boxplot diagrams indicating median values, standard deviation, and 95% confidence intervals.

Abbildungen 3a und 3b. Kumulative Zahl der Einnahmetage von a) Ciclosporin A und b) Aciclovir in der frühen Posttransplantationsphase bei Kindern mit (grau) und ohne (weiß) renale Dysfunktion. Dargestellt sind Medianwerte, Standardabweichung und 95%-Vertrauensbereiche.

Results

After SCT an episode of renal dysfunction was observed in twelve children (28%) after a median of 2 months (range, 1–10 months). In all but one patient (including the child with preexisting nephropathy) renal dysfunction was transient with a median time to complete recovery of 8 months (range, 3–16 months). One single patient (9-year-old girl with acute myeloid leukemia) developed persistent renal dysfunction with onset at 10 months after SCT. The individual serum creatinine values as a function of time are depicted in Figure 1.

The actuarial 3-year freedom from persistent renal toxicity for children surviving > 12 months after SCT was 97.3%. According to the Common Terminology Criteria CTCAE v3.0, late renal toxicity grade 1 was observed in nine children (21%) and grade 2 in three children (7%). No grade 3/4 toxicities occurred. None of the patients with renal dysfunction required dialysis at any time. Four children died during follow-up including the child with persistent renal dysfunction due to recurrent malignant disease. Renal dysfunction-free survival was independent of the TBI dose regimens applied (Figure 2). Neither acute nor chronic GVHD had significant influence on renal dysfunction-free survival (acute p = 0.361, chronic p = 0.234).

In our patients, we found no correlation between development of renal dysfunction and treatment duration with potentially nephrotoxic drugs like cyclosporine A, acyclovir, aminoglycosides or vancomycin. Cumulative application days of cyclosporine A and acyclovir in patients with and without renal dysfunction are shown in Figure 3.

No other patient- and treatment-related variables had significant influence on development of renal dysfunction in univariate$_1$ or multivariate$_2$ analysis: gender ($p_1 = 0.116$, $p_2 = 0.207$), remission status at SCT ($p_1 = 0.115$, $p_2 = 0.187$), diagnosis ($p_1 = 0.346$, $p_2 = 0.292$), chemotherapy regimen ($p_1 = 0.660$, $p_2 = 0.590$), single dose of TBI ($p_1 = 0.893$, $p_2 = 0.926$), and relapse after SCT ($p_1 = 0.110$, $p_2 = 0.118$).

Discussion

TBI continues to be an important part of the conditioning regimen before SCT [2, 15, 26]. The growing number of long-term survivors after SCT has put more attention onto long-term side effects such as renal impairment. Espe-

Table 2. Published data reporting on renal dose and incidence of renal dysfunction after fractionated total-body irradiation.
Tabelle 2. Literaturübersicht zur Dosisabhängigkeit der renalen Dysfunktion nach fraktionierter Ganzkörperbestrahlung.

Study	Patients (n)	Age (median) (years)	Renal dose total (Gy)	Renal dose per fraction (Gy)	Renal dysfunction (%)	Persistent renal dysfunction n (%)	Late renal toxicity grade I–IV (n)	Follow-up median (months)
Miralbell et al. [21]	79	3–56	10	1.66	5	Not stated	Not stated	18
		(32.5)	12	2.0	26			
			13.5	2.25	45			
Chou et al. [7]	58	0.9–18	12	2.0	3	2 (3)	I/II: 1	56
		(8.4)					III: 1	
Borg et al. [5]	59	1–70	12	2.0	15	2 (3)	I: 1	29
		(50)					II: 2	
Miralbell et al. [22]	71	17–61	10	1.66	50	Not stated	Not stated	32
		(41)	12	2.0	41			
			13.5	2.25	14			
Esiashvili et al. [11]	60	0.3–19.6	4–12	1.75–2.0	28.6	2 (3)	I: 1	4.5
		(8.4)	13–14	1.75	20	7 (12)	II: 3	
							III: 3	
							IV: 2	
Own data	43	3–16	≤ 11.1	1.5–1.7	22		I: 9	51
		(11)	12	1.5–3.0	32	1 (2)	II: 3	

cially in children, only limited data exist regarding late effects of TBI on renal function. Young age, multiagent chemotherapy and potentially nephrotoxic drugs negatively impact on renal tolerance to TBI [5, 7, 9].

BMT (bone marrow transplantation) nephropathy is defined as chronic renal dysfunction occurring approximately 8–12 months after SCT, although in children, a latency period of only 3–6 months has also been described [5, 8, 13]. Radiation-induced renal damage is a process of sclerosis and occlusion of kidney arterioles with secondary degeneration of glomeruli and tubules resulting in interstitial renal fibrosis [12, 23]. The spectrum of renal toxicity reaches from slight increase of the serum creatinine up to progressive renal insufficiency requiring dialysis [1, 8, 16, 21, 22]. Due to different definitions, incidence of BMT nephropathy varies from 3% to 50% without age-specific analysis in most reports [5, 7, 20–22].

In this analysis, renal toxicity was based on the serum creatinine level only due to its availability at different time points in all patients. Although minor renal function impairments may have been missed, one can assume that clinically relevant renal dysfunctions have been detected by this method, because a decrease in glomerular filtration rate almost always leads to an increase in serum creatinine level in young children [21].

While in adults renal tolerance after fractionated TBI has been estimated to be 14 Gy, in children it was assumed to be ≤ 12 Gy [9]. Miralbell et al. [21] reported on 79 patients with 10, 12, and 13.5 Gy of fractionated TBI and found a significant increase of chronic nephropathy after 18 months at a rate of 5%, 26%, and 45%, respectively. A dose-response relationship was postulated as well by Cheng et al. [6] and Kal & van Kempen-Harteveld [17]. Contrarily, in a later report, Miralbell et al. [22] described an inverse correlation between TBI dose and incidence of renal dysfunction. However, in this analysis nephropathy correlated with application of potentially nephrotoxic contrast agents as well as nephrotoxic drugs in the lower-renal-dose group.

In our analysis, we found a TBI dose of ≤ 12 Gy to rarely cause persistent nephropathy in children. We also could not find single dose to correlate with the incidence of renal dysfunction either. Accordingly, Röttinger et al. [25] and Kist-van Holthe et al. [19] noted that BMT nephropathy was rare when doses of fractionated TBI did not exceed 12 Gy. An overview of the literature including our own data is given in Table 2.

The potential benefit of renal shielding has been reported in recent publications. Igaki et al. [16] found a dose-response relationship for renal insufficiency among 109 patients between 5–54 years. By partial shielding, renal dose was limited to 10 Gy in six fractions of 1.7 Gy. Selective renal shielding increased renal dysfunction-free survival from 78.5% (12 Gy) to 100% (10 Gy) after 24 months. Lawton et al. [20] similarly reported a protective effect of partial renal shielding. Limiting renal doses to 9.8 and 11.9 Gy by partial shielding reduced the risk of chronic nephropathy after 30 months to 0% and 14.1% compared to 29.4% after 14 Gy without renal shielding. Several authors postulated that in children and patients with preexisting renal impairment the cumulative renal dose of fractionated TBI should be limited to 10 Gy [5, 17, 21].

Potential nephrotoxic drugs such as cyclosporine may impact on late renal dysfunction [6, 22]. Frisk et al. [13] found that seven of 26 patients (27%) with chronic renal impairment after SCT had received more nephrotoxic antibiotics during early posttransplant period. In our analysis, we did not find a

correlation between renal dysfunction and cumulative application days of potentially nephrotoxic drugs like cyclosporine A and acyclovir. In accordance with other authors [5, 11, 14] we did not find GVHD to be a risk factor for renal insufficiency.

Conclusion

In this analysis, the incidence of persistent renal dysfunction after fractionated TBI with total doses ≤ 12 Gy was very low and, thus, this regimen appears to be safe. We continue to limit kidney doses to 10 Gy by customized renal shielding for patients with a history of renal dysfunction prior to SCT.

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