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Original Article

Total Body Irradiation (TBI) in Pediatric Patients

A Single-center Experience after 30 Years of Low-dose Rate Irradiation

Claudia Linsenmeier[1], Daniel Thoennessen[1], Laura Negretti[1], Jean-Pierre Bourquin[2], Tino Streller[1], Urs Martin Lütolf[1], Susanne Oertel[1,3]

Purpose: To retrospectively analyze patient characteristics, treatment, and treatment outcome of pediatric patients with hematologic diseases treated with total body irradiation (TBI) between 1978 and 2006.
Patients and Methods: 32 pediatric patients were referred to the Department of Radiation-Oncology at the University of Zurich for TBI. Records of regular follow-up of 28 patients were available for review. Patient characteristics as well as treatment outcome regarding local control and overall survival were assessed. A total of 18 patients suffered from acute lymphoblastic leukemia (ALL), 5 from acute and 2 from chronic myelogenous leukemia, 1 from non-Hodgkin lymphoma, and 2 from anaplastic anemia. The cohort consisted of 15 patients referred after first remission and 13 patients with relapsed leukemia. Mean follow-up was 34 months (2–196 months) with 15 patients alive at the time of last follow-up. Eight patients died of recurrent disease, 1 of graft vs. host reaction, 2 of sepsis, and 2 patients died of a secondary malignancy.
Results: The 5-year overall survival rate (OS) was 60%. Overall survival was significantly inferior in patients treated after relapse compared to those treated for newly diagnosed leukemia (24% versus 74%; p=0.004). At the time of last follow-up, 11 patients survived for more than 36 months following TBI. Late effects (RTOG $\geq$3) were pneumonitis in 1 patient, chronic bronchitis in 1 patient, cardiomyopathy in 2 patients, severe cataractogenesis in 1 patient (48 months after TBI with 10 Gy in a single dose) and secondary malignancies in 2 patients (36 and 190 months after TBI). Growth disturbances were observed in all patients treated prepubertally. In 2 patients with identical twins treated at ages 2 and 7, a loss of 8% in final height of the treated twin was observed.
Conclusion: As severe late sequelae after TBI, we observed 2 secondary malignancies in 11 patients who survived in excess of 36 months. However, long-term morbidity is moderate following treatment with the fractionated TBI at the low-dose rate that was generally used here. Conditioning for bone marrow transplantation without radiation is an attractive option, but is not sufficiently effective to completely replace TBI for the most common pediatric indications.

Key Words: Total body irradiation · Stem cell transplantation · Low-dose rate irradiation

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Ganzkörperbestrahlung (TBI) in der Pädiatrie – 30 Jahre Erfahrungen mit Niedrig-Dosisraten-Bestrahlung

Ziel: Retrospektive Analyse von Patientencharakteristika, Behandlung und Ergebnis bei Kindern mit hämatologischen Erkrankungen, die zwischen 1978 und 2006 mit Ganzkörperbestrahlung behandelt wurden.
Patienten und Methodik: 32 Kinder wurden unserer Klinik zur TBI zugewiesen, 28 Krankengeschichten waren zugänglich (n=28). 18 Patienten litten unter akuter lymphoblastischer Leukämie (ALL), 5 unter akuter (AML) und 2 unter chronisch myeloischer Leukämie (CML), einer unter Non-Hodgkin-Lymphom und zwei unter aplastischer Anämie. 15 Patienten wurden nach erster Remission zugewiesen, 13 mit Rezidiv. Bei der letzten Kontrolle lebten noch 15 Patienten (mean 34 Monate (2–196 Monate). Acht Patienten sind an einem Rezidiv verstorben, einer an einer Graft-versus-host Erkrankung, zwei an Sepsis und zwei an Sekundärtumoren.
Resultate: Das 5-Jahres Gesamtüberleben lag bei 60%. Das Gesamtüberleben war signifikant (p=0.004) niedriger bei Patienten, die nach einem Rezidiv behandelt wurden (24%), als bei solchen die bei Erstdiagnose behandelt wurden (74%). Spättoxizität RTOG >=3 waren eine Pneumonitis bei 1 Patienten, eine chronische Bronchitis bei einem Patienten, Kardiomyopathie bei 2 Patienten, eine Katarakt bei einem Patienten (48 Monate nach TBI mit 10Gy Einzeldosis) und Sekundärtumore bei 2 Patienten.

[1]Department of Radiation-Oncology – University Hospital Zurich, Switzerland,
[2]University Children's Hospital Zurich, Department of Hemato-Oncology,
[3]Department of Radiation Oncology – University of Heidelberg, Germany.

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Wachstumsstörungen mit einer Körpergrösse kleiner als die 25. Perzentile zeigten sich bei allen vor der Pubertät behandelten Kindern. Bei zwei eineiigen Zwillingen zeigt sich ein Verlust von 8% an Körpergrösse im Vergleich zum Zwilling.

Schlussfolgerung: Wie erwartet zeigen sich schwere Spättoxizitäten nach Ganzkörperbestrahlung mit zwei Sekundärtumoren bei 11 Patienten, die länger als 36 Monate überlebt haben. Aber die Morbidität ist mässig nach fraktionierter Ganzkörperbestrahlung und der hier in fast allen Fällen verwendeten niedrigen Dosisrate. Konditionierung ohne TBI ist eine attraktive Möglichkeit, aber noch nicht effektiv genug um die TBI im Kindesalter ganz zu ersetzen.

Schlüsselwörter: Ganzkörperbestrahlung · Stammzelltransplantation · Dosisrate

Introduction

Hematopoetic stem cell transplantation is the treatment of choice for many hematological malignancies. Since the first successful bone marrow transplantations in the 1950s, total body irradiation (TBI) remained the mainstay of conditioning regimens until the late 1980s in both pediatric and adult patients [14, 22]. In the late 1970s, the technique changed from high-dose single fractions to fractionated regimens [20]. The incidence of the often lethal veno-occlusive disease (VOD) of the liver was dramatically reduced with fractionated regimens [11, 12]. In the 1980s, dose rates were reduced resulting in a further decrease in late effects, especially cataractogenesis, renal toxicity, and interstitial pneumonitis [1, 7, 16] . Nevertheless, severe long-term sequelae, especially the induction of secondary malignancy, hormonal dysregulation, reproductive insufficiency, as well as growth retardation and the development of osteochondromas in pediatric patients remained an issue [15, 21, 23, 29].

In the 1990s, a couple of prospective randomized studies were initiated in which TBI was compared to chemotherapy-only regimens, usually based on busulfan and cyclophosphamide. However, TBI proved to be superior as far as overall survival (OS), disease-free survival (DFS), graft vs. host reaction (GvHR) and VOD incidence were concerned [5, 6, 13, 17, 28]. Therefore, total body irradiation has remained the cornerstone of conditioning regimens in pediatric hematologic diseases [30] despite the risk of possible late consequences.

The TBI technique differs dramatically between institutions. Most essential is the generation of one homogenous large field in order to prevent overdosage due to overlapping adjacent fields. Irregularities of body contour, tissue heterogeneity, and the difficulties of internal scatter impose major radiation delivery and treatment planning difficulties [8]. The applied TBI technique and its dosimetry, however, significantly affect the success of bone marrow transplantation (BMT) and the rate of complications [18, 22].

We reviewed the records of our pediatric patients treated with TBI at the University Hospital of Zurich from 1978–2006 in order to analyze treatment outcome and late sequelae.

Patients and Methods

Since 1978, 32 pediatric patients (referred from the University Children's Hospital Zurich) were treated with TBI at our institution. All patients have been treated according to standard protocols of the BFM (Berlin–Frankfurt–Münster study group) or SPOG (Swiss pediatric oncology group). Patients' characteristics are provided in Table 1.

Records of regular follow-up of 28 patients were available for review. Mean follow-up (FU) was 34 months (range 2–196 months). At the time of last FU, 15 patients were alive, while 8 had died of a recurrence, 1 of a GvHR, 2 of sepsis, and 2 patients died of secondary malignancy. Mean FU of the surviving 15 children was 56 months (12–171 months). At the time of last FU, 11 patients had survived TBI for more than 36 months.

Of the patients, 18 suffered from acute lymphoblastic leukemia (ALL), 5 from acute and 2 from chronic myelogenous leukemia, 1 from non-Hodgkin lymphoma, and 2 from anaplastic anemia. A total of 15 patients were referred after first remission and 13 patients with relapsed leukemia. Mean age at the time of TBI was 10 years (range 2–17 years). Transplantations with bone marrow from a related donor was performed in 13 children, 2 of whom were monozygotic twins, while 8 children received bone marrow from HLA-identical unrelated donors and 6 received peripheral stem cells from related donors.

All but 2 patients (n=26) underwent fractionated TBI in single doses of 2–2.2 Gy up to total doses of 12–13.2 Gy, administered either once (12 patients) or twice daily (14 patients) at a mean low dose rate of 0.06 Gy/min (range 0.04–0.1 Gy). The other two patients (n=2) had been treated in the late 1970s and received 10 Gy in a single fraction at dose rates of 0.15 Gy/min and 0.035 Gy/min, respectively, resulting in an overall treatment time of more than 4 hours in the latter patient.

The lungs were shielded with individualized partial transmission lung blocks in order to reduce lung doses to $\leq$10 Gy. Thermoluminescence dosimetry (TLD) to the head, neck, jugulum, xiphoid, and navel were applied during at least two fractions. No eye shielding was performed.

One child with c-ALL received an additional boost to the mediastinum of 3x2 Gy. Five children with ALL received an additional boost to the testes of 3x2 Gy or 11x1.2 Gy, 3 of them also received a boost to the brain (3x2 Gy). Three children had received irradiation to the brain before TBI was indicated.

Follow-up examinations after TBI were routinely performed in the Department of Pediatric Oncology and included clinical assessment with measurement of height and weight, blood counts (including differential blood, kidney, and liver parameters), hormonal status at least once yearly, chest X-ray, electrocardiogram, and an ophthalmological control in case of

Table 1. Characteristics of treated patients. m: male, f: female, ALL: acute lymphoblastic leukemia, AML: acute myelogenous leukemia, CML: chronic myelogenous leukemia, NHL: non-Hodgkin lymphoma, AA: anaplastic anemia, TBI: total body irradiation.

Tabelle 1. Charakteristik der behandelten Patienten.

Gender	Diagnosis	Relapsed leukemia at time of TBI	Age at time of TBI	Transplantation	Single dose	Total dose	GV HD	Secondary malignoma	Recurrence	Death	Follow-up (months)	Late effects
m	ALL	+	11	allogeneic bone marrow	2	12		M. Hodgkin	1	1	8	secondary malignancy
m	AML		17	allogeneic bone marrow	2	12		0	0	0	87	
m	ALL	+	5	allogeneic bone marrow	10	10		0	1	1 (recurrence)	14	
m	AML	+	2	allogeneic bone marrow (identical twin)	10	10		Fibrosarcoma Colon	0	1	196	secondary malignancy cataract
m	ALL	+	7	allogeneic bone marrow	2	12		0	1	1 (recurrence)	35	
m	ALL		17	allogeneic bone marrow	2	12				0	171	
m	ALL		7	allogeneic bone marrow (identical twin)	2	12		0	0	0	170	cardiomyopathia
m	ALL	+	12	allogeneic bone marrow	2	12		0	1	1 (recurrence)	29	pneumonitis
m	NHL		17	allogeneic bone marrow	2	12	+	0	0	0	121	
f	AML		16	allogeneic bone marrow (not related)	2.2	13.2		0	0	0	108	cataract
m	CML		11	allogeneic bone marrow (not related)	2	12		0	1	1 (recurrence)	97	hypothyreosis
m	ALL		12	allogeneic bone marrow	2	12	+	0	0	1 (sepsis)	2	
m	ALL		17	allogeneic bone marrow	2	12	+	0	0	0	83	
f	AA	+	8	allogeneic hematopoietic stem cell	2	6		0	1	1 (recurrence)	19	
f	AA		17	allogeneic bone marrow (not related)	2	12		0	0	0	62	glomerular nephritis
m	CML		17	allogeneic bone marrow (not related)	2.2	13.2	+	0	0	0	60	elevated liver enzymes chronic bronchitis
f	ALL		8	allogeneic hematopoietic stem cell	2	12		0	0	0	53	special school
m	ALL	+	7	allogeneic bone marrow (not related)	2	12		0	0	0	35	glomerular nephritis
f	ALL	+	3		2	12		0	1	1 (recurrence)	6	

Table 1. (continued)

Table 1. (Fortsetzung)

Gender	Diagnosis	Relapsed leukemia at time of TBI	Age at time of TBI	Transplantation	Single dose	Total dose	GV HD	Secondary malignoma	Recurrence	Death	Follow-up (months)	Late effects
m	ALL		3	allogeneic hematopoietic stem cell	2	12		0	0	0	33	glomerular nephritis
m	ALL	+	11	allogeneic hematopoietic stem cell	2	12		0	1	1 (recurrence)	7	
f	AML	+	12	allogeneic bone marrow (not related)	2	12		0	0	0	34	cardiomyopathy
m	ALL		6	allogeneic bone marrow (not related)	2	12		0	0	0	28	
m	ALL	+	12	allogeneic hematopoietic stem cell	2	12		0	1	1 (recurrence)	10	hypothyreosis
m	ALL	+	12	allogeneic bone marrow (not related)	2	12	+	0	0	0	19	elevated liver enzymes
m	AML		8	allogeneic bone marrow	2	12	+	0	0	0	11	
m	ALL	+	5	allogeneic hematopoietic stem cell	2	12	+	0	0	1 (sepsis)	3	
m	ALL		13	allogeneic bone marrow	2	12		0	0	0	9	optic nerve edema

subjective clinical impairment. In addition, surviving patients and the parents of 6 patients who had been lost to follow-up were contacted and questioned.

The end point selected for the retrospective analysis was overall survival (OS). Statistica version 5.5 (StatSoft, Tulsa, OK, USA) was used for statistical analysis. Overall survival was calculated from the time of first radiation fraction to the date of death or to the date of last FU. Patterns of survival were estimated by the Kaplan–Meier method. Differences between groups were assessed by log rank test (2 groups) and X^2 test (more than two groups).

Results

The 5-year OS was 60% (Figure 1); however, overall survival was significantly inferior in patients treated after relapse compared to those treated for newly diagnosed leukemia (24% versus 74% p=0.004; Figure 2). There was a trend towards improved survival in patients treated with TBI for ALL compared to AML with a 5-year OS rate of 68% versus 46% (p=0.11). Interestingly, survival was better in those patients who had received a matched unrelated bone marrow transplant, compared to those who were administered bone marrow or peripheral stem cells of related donors, with 5-year OS of 88% versus 57% and 33%, respectively. This difference was, however, not significant (p=0.14; Figure 3). Mean time of aplasia after TBI was 22 days. GvHR were observed in 7 patients and were temporarily severe in 3. Of the severe reac-

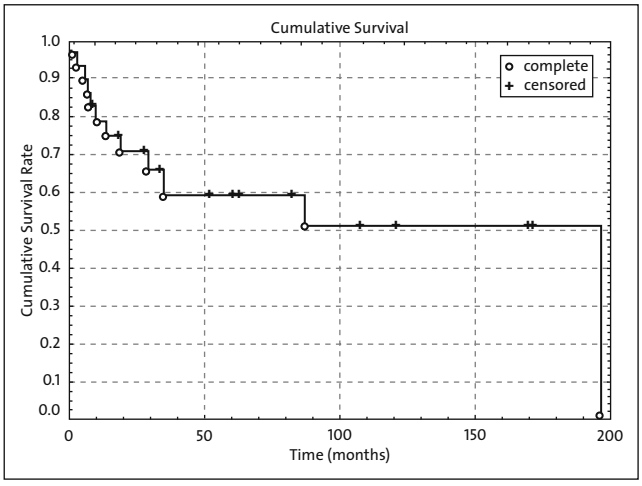

Figure 1. Overall survival after TBI in pediatric patients.

Abbildung 1. Gesamtüberleben nach Ganzkörperbestrahlung bei pädiatrischen Patienten.

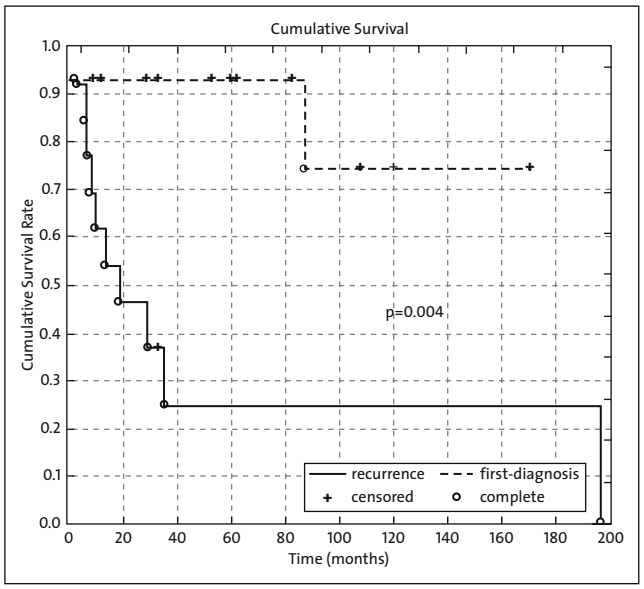

Figure 2. Overall survival after TBI for first diagnosis or recurrent disease.

Abbildung 2. Gesamtüberleben nach Ganzkörperbestrahlung bei Erstdiagnose oder nach Rezidiv.

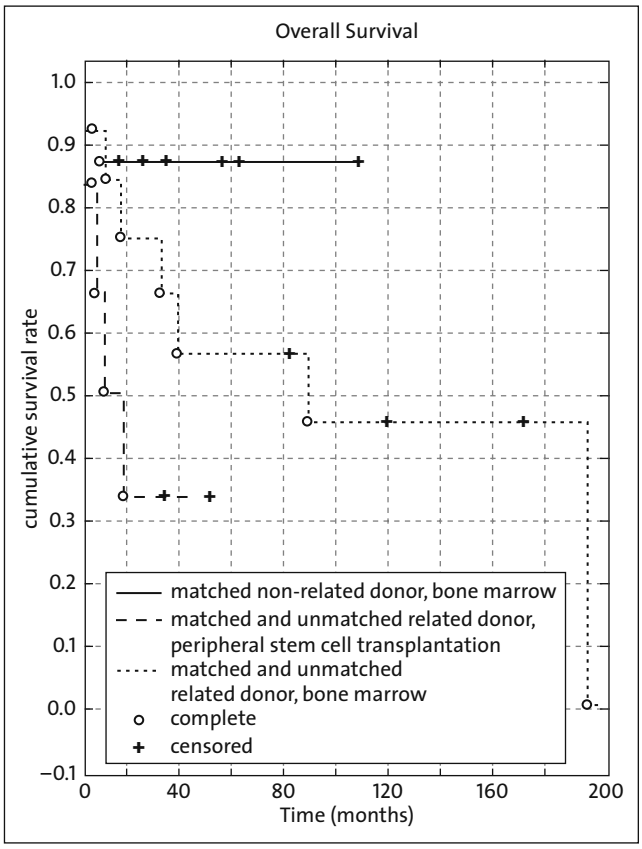

Figure 3. Overall survival after matched non-related donor and related donor (p=n.s.).

Abbildung 3. Überleben nach Transplantation mit passendem nichtverwandtem und verwandtem Spender (p=n.s.).

tions, 1 patient died within 4 weeks after transplantation of a candida sepsis during severe GvHR of the gastrointestinal tract. In 5 patients, chronic GvHR with associated slight skin reactions were recorded. The cumulative incidence of chronic GvHR reached 25% after 5 years.

Subacute effects observed were a nonfatal pneumonitis in one of the 2 patients treated with a single dose TBI and 2 cases of severe acute parotitis requiring pain medication. One patient developed edema of the optic nerves within 2 months after TBI which lead to impaired sight in one eye.

Late effects (RTOG ≥3) observed were chronic bronchitis in 1 patient, cardiomyopathy in 2 patients, and severe cataractogenesis requiring surgery in 1 patient (48 months after TBI with 10 Gy in a single dose). Elevated kidney parameters with slight glomerular nephritis were observed in 3 patients. Elevated liver enzymes could be observed in 2 patients with GvHR.

Two children required hormones for hypothyroidism. All girls treated before the onset of puberty demonstrated elevated FSH levels and 1 required hormones to induce puberty. IgF-1 was low in all patients treated before puberty, but growth hormones were required in only 2 patients. One patient was not able to attend normal school and had to be transferred to a special school. The other patients attended and graduated from normal schools. Growth disturbances (defined as a height in the lower 25th percentile) were observed in all patients treated prepubertally. In 2 patients with identical twins, treated at age 2 and 7 years, a loss of 8% in final height was observed compared to their untreated twins. No problems with dentition were reported. Secondary malignancies occurred in 2 patients (Hodgkins disease 36 months after TBI and a gastrointestinal fibrosarcoma 190 months after TBI).

Discussion

With a 5-year OS of 60% in all treated patients and 10-year OS rate of 74 % in those patients undergoing TBI after their first remission, our data compare well with the literature [5, 10, 13, 24]. There are four prospective randomized studies comparing TBI with chemotherapy-only conditioning regimens: Blaise [5] reported OS rates of 75% after cyclophosphamide (Cy)/TBI conditioning versus 51% after chemotherapy-only (Busulfan (Bu)/Cy) conditioning in 101 patients treated for AML in first remission. Ringden [24] reported for the Nordic Bone Marrow Transplantation Group a 3-year survival rate of 76% after conditioning with TBI/Cy compared to 62% after conditioning with Bu/Cy in 167 patients with leukemia (~40% AML, 35% CML, 25% ALL). Seattle [10] and the French Society of Bone Marrow transplantation [13] found no difference or clear advantages for either regimen (Cy/TBI versus Cy/BU) in patients with CML and reported a 3-year OS rate of 80% and a 5-year OS rate of about 60%. Granados et al. [17] report on

a retrospective analysis of 156 patients with ALL transplanted after either TBI-based or chemotherapy-only conditioning and found a statistically significant improved 6-year event-free survival of 43% versus 22% favoring the TBI regimen. Despite the well-known late sequelae, TBI-based regimens continue to be widely accepted, especially in ALL (above the age of 2 years) and remain the mainstay in conditioning treatment.

Side effects and complications of TBI have been extensively studied and yet remain difficult to distinguish from side effects of high-dose chemotherapy. In pediatric patients, especially high rates of late sequelae following TBI have been observed in studies with long median follow-up times of over 3 years [23, 29]. Consistent with our data, hypothyroidism was observed in 12% of pediatric patients after a median FU of 3 years. After a median FU of 12 years, mild cataracts were recorded in 80% of patients, while severe cataracts were observed in 20% after 6 years. However, in leukemia patients cataract incidence is also influenced by cortisone medication and was observed in 12% of AML patients treated without TBI [28].

Interestingly, we detected no clinically or radiologically relevant interstitial pneumonitis (IP) in low-dose TBI and only one case of chronic bronchiolitis. TBI with lung shielding and reduced dose rates in other retrospective analyses resulted in IP rates as low as 2% [26, 27]. Busulfan is also known to impair lung function and resulted in lower mean vital capacities than fractionated TBI in a retrospective analysis of 80 children after a median follow-up of 4 years [9]. Compared to these data, the incidence of late side effects in our 11 long-term survivors treated with low-dose rate TBI remains low, with only one cataract and two clinically manifest cases of hypothyroidism. The cases of cardiomyopathy, interstitial bronchiolitis, and decreased glomerular filtration rates are also possibly attributable to chemotherapy.

With respect to organ dysfunction, long-term morbidity and mortality, the Bone Marrow Transplant Survivor Study [3] demonstrated a protective effect provided by TBI compared to the chemotherapy-only regimen in over 850 patients who had survived autologous hematopoietic stem cell transplantation for more than 2 years. Robin et al. [25] found that TBI, compared to chemotherapy-only conditioning, was mainly associated with cataracts, endocrine dysfunction, secondary cancers, and late severe bacterial infection, whereas pulmonary and cardiac problems seemed to be associated with chemotherapy and GvHR. There were no cases of late severe bacterial infections in our small cohort of long-term survivors, but 2 patients died secondary to sepsis during the time of aplasia. In addition, aplasia duration in our patients and in the literature was not longer than after conditioning regimens without TBI. We found reduced glomerular filtration rates in 3 patients, which were most likely induced by chemotherapy. Miralbell et al. [19] actually reported an inverse correlation between renal function and the prescribed TBI dose, and attributed this to the use of nephrotoxic contrast agents at the time of treatment planning with the aim of improving kidney shielding. Hypothyroidism is a common late sequela of conditioning with and without TBI and has been observed in over 70% of patients 5 years after TBI; supplementation was necessary in 10% of those affected [2], which is consistent with our findings.

Two of our patients died as a result of secondary malignancies – one hematological disease which occurred earlier and one solid tumor which occurred more than 10 years after transplantation. Recently published data about secondary cancer after TBI showed a cumulative incidence of solid tumors of 1.7% and 8.2% after 5 and 10 years, respectively [21]. Bhatia et al. [4] observed a cumulative incidence of 10% for solid cancer 10 years after conditioning with and without TBI, with a higher risk for younger patients and a higher risk for certain cancers, e.g., thyroid, oral cavity, liver cancer, in patients receiving radiation therapy. Our patients definitely remain at a life-long high risk for secondary cancers and should attend careful screening.

Conclusion

Low-dose rate TBI using conventional fractionation results in acceptable early and late toxicity with a demonstrated low risk for cataracts, interstitial pneumonitis, and veno-occlusive disease. It also yields favorable OS rates. Therefore, despite its late sequelae, TBI remains warranted in certain pediatric patients (over 2 years of age) undergoing transplantation, given that chemotherapy-only conditioning regimens have not proven to be equally effective in the current literature. Ongoing studies may show a paradigm shift in the future. Obviously, conditioning with TBI or chemotherapy for bone marrow transplantation in pediatric patients should be exclusively performed within studies and at specialized centers.

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Address for Correspondence
Dr. med. C. Linsenmeier
Department of Radiation Oncology
University Hospital Zurich
Rämistr. 100
8091 Zurich
Switzerland
Phone (+41) 44-255-2931, Fax -4547
e-mail: claudia.linsenmeier@usz.ch