Late Toxicity in Children Undergoing Hematopoietic Stem Cell Transplantation with TBI-containing Conditioning Regimens for Hematological Malignancies

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Introduction

Myelo-ablative hematopoietic stem cell transplantation (HSCT) is the treatment of choice for several malignant childhood hematologic disorders [11, 19]. Long-term survivors are considerably increasing, not only due to the substantial improvements in supportive care, but also to progressively more accurate patients selection and treatment protocols optimization. Conventional myelo-ablative conditioning regimens consist of a combination of high-dose chemotherapy plus/minus total-body irradiation (TBI). In spite of its efficacy, TBI may potentially expose patients to the risk of normal tissues radiation-induced injury; hereby, major concerns are late or very late toxic effects that might potentially worsen health status and quality of life after HSCT [3, 6, 15, 17].

Herein we report on our experience in a cohort of very long-term survivors affected with childhood leukemia or lymphoma treated with TBI and subsequent HSCT.

Patients and Methods

Fifty-one patients, disease-free at least at 5 years from HSCT, were included in the present study. General patients characteristics, type of transplantation, stem cell source, TBI dose and fractionation and chemotherapy are summarized in Table 1. The median time interval from diagnosis to HSCT was 1.2 years (range 0.3- 3.6), since roughly 50% of patients were transplanted in first complete remission.

Total-body irradiation: TBI was delivered via anterior-posterior parallel opposed fields, with 6 MV or 18 MV energy photons. Customized lung shields were used to reduce total lung dose. The dose prescription point was on beam's central axis, localized at umbilical height. Patients were treated in semi-standing position, with a dedicated positioning device, at a skin-axis distance of 3.8-4.4 meters. Median dose-rate was 15-18 cGy/min. Children aged < 3 years were treated in supine position, under general anesthesia and with a hypo-fractionated schedule.

Chemotherapy associated to TBI and GvHD prophylaxis:
As shown in Table 1, several heterogeneous chemotherapy regimens were employed as conditioning with TBI, depending on disease, status at transplantation, auto/allo-transplantation. GvHD prophylaxis consisted of the administration of Cyclosporine-A for all patients, alone or in association with Methotrexate and/or Anti-Thymocite Globulin and/or Prednisone.

Follow-up protocol: Every patient underwent a pre-transplantation clinical and biochemical prospective work-up, including endocrinologic, pulmonary and ophthalmologic evaluation.
Thyroid function:
– Yearly measurement of basal TSH and free-thyroxin (f-T4)
– Thyrothropin test (carried out to evaluate TSH secretion only in case of suspected central hypothyroidism)
– Ultrasonographic evaluation every 2 years to assess thyroid volume and echogenic pattern (if suspicious nodules: plasma thyroglobulin levels and FNA)

Thyroid dysfunction was defined as follows:
– Primary hypothyroidism: raised basal serum TSH level, with normal (compensated) or reduced (overt) f-T4 levels
– Central hypothyroidism: defined as reduced f-T4 levels, with normal or reduced TSH levels, and blunted TSH peak after TRH test

Growth velocity: Height was measured every year by Harpenden stadiometer (every 6 months if growth delay). Growth velocity was compared to the age-adjusted centiles (*Sempe and Pedron curves*). When growth velocity was < 1.5 SD for 2 years or <2 SD for 1 year, other evaluations (serum somatomedins-IGF1, basal and after stimulus GH secretion) were then performed. Target genetic height was taken into account for final evaluation.

Gonadal function: Each pubertal patient underwent a clinical endocrinologic evaluation according to Tanner Criteria every 6 months and a yearly determination of basal levels of FSH, LH, total testosterone for males and 17-beta estradiol for females.

Gonadal dysfunction was defined as follows:
– Hypergonadothropic hypogonadism: increase in LH/FSH levels with decreased sexual hormones

Key Words: Total-body irradiation · Hematopoietic stem cell transplantation · Toxicity · Childhood malignancies

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Table 1. Patients characteristics. ALL: Acute Lymphoblastic Leukemia; AML: Acute Mieloyd Leukemia; CML: Chronic Myeloid Leukemia; NHL: non-Hodgkin Lymphoma, CR: Complete Remission; SIB: Sibling, REL: Related, MUD: Matched Unrelated Donor; BM: Bone Marrow; PBSC: Peripheral Blood Stem Cells; UCB: Umbilical Cord Blood; VP16: Etoposide; CTX: Cyclophosphamide; L-PAM: Melphalan; VCR: Vincristine; ARA-C: Cytosine Arabinoside; TT: Thiotepa; FLUDARA: Fludarabine.

Patients	Total Number	51
	Males	32/51 (62.7%)
	Females	19/51 (37.3%)
Median age at HSCT	8.5 years (range: 2–16.4 years)	
Diagnosis	ALL	32/51 (62.7%)
	AML	15/51 (29.4%)
	CML	2/51 (3.9%)
	NHL	2/51 (3.9%)
Disease status at HSCT	CR1	21/51 (41.2%)
	CR2	23/51 (45.1%)
	CR3	4/51 (7.8%)
	Active disease	1/51 (1.9%)
	Chronic phase	2/51 (3.9%)
Type of HSCT	Autologous	12/51 (23.5%)
	Autologous purged	7/51 (13.7%)
	Allogeneic SIB	17/51 (33.3%)
	Allogeneic REL	2/51 (3.9%)
	Allogeneic MUD	13/51 (25.5%)
Graft Source	BM	35/51 (68.6%)
	PBSC	10/51 (19.6%)
	UCB	6/51 (11.8%)
TBI dose	TBI 1440 cGy	6/51 (11.8%)
	TBI 1200 cGy	42/51 (82.4%)
	TBI 990 cGy	3/51 (5.6%)
Chemotherapy associated to TBI	VP16-CTX	10/51 (19.6%)
	L-PAM	10/51 (19.6%)
	VCR-CTX	6/51 (11.8%)
	VP16	8/51 (15.7%)
	ARA-C	2/51 (3.9%)
	CTX	3/51 (5.6%)
	CTX-TT	9/51 (17.6%)
	FLUDARA-TT	3/51 (5.9%)

– Hypogonadothropic hypogonadism: decrease in LH/FSH levels with decreased sexual hormones
– Testicular germinal dysfunction: FSH value above normal ranges for age

Pulmonary function: Pulmonary function tests were performed on compliant patients older than 6 years, yearly in asymptomatic patients and every 6 months in symptomatic patients (dyspnea, cough). The following parameters were considered for the study: forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC)

Pulmonary dysfunction was defined as follows:
– Normal: if FVC and FEV1 were both >80% of predicted value
– Mild restrictive disease: if FEV1 was >80% and FVC was between 70% and 79%
– Severe restrictive disease: if FEV1 was >80% and FVC <70%
– Obstructive disease: if FEV1 was <80% and FVC was normal

Ophthalmologic evaluation: Yearly slit-lamp examination was performed for detection of eye-lens opacities. Mild cataract was defined as the presence of sub-capsular opacities not interfering with visual acuity, while severe cataract as the presence of subcapsular opacities interfering with visual acuity and requiring surgery.

Statistical analysis: Actuarial rate of incidence and severity of late toxic effects on endocrine system, lung, eye as well as second malignancies cumulative incidence were estimated by Kaplan-Meier method, with Log Rank test. Univariate analysis was carried out by Pearson χ^2 and Fisher exact test. Continuous variables were evaluated by Student's T test for independent samples.

Results

Median follow-up is 8.6 years (range: 5.1-17.9 years). Fourteen patients (out of 32 allogeneic HSCT) developed chronic GvHD.

Thyroid dysfunction: Evaluable patients: 47. Hypothyroidism was diagnosed in 10 patients (21.2%) at a median onset time of 3 years after transplantation: 2 patients developed compensated, 4 overt and 4 central hypothyroidism (3/4 previously treated with 18 Gy CNS prophylaxis). Ten-year cumulative risk of hypothyroidism is 21.8% (SE=0.06). Three patients presented benign nodules (6.4%). Ten-year cumulative risk of developing benign thyroid nodules is 10.6% (SE=0.06).

Growth impairment: Evaluable patients: 50. Twelve patients showed severe growth impairment requiring GH replacement therapy (24%). The cumulative risk of severe growth impairment is 29.9% (SE = 0.008) at 10 years. Younger patients have a significant higher incidence of delayed growth velocity (T-Student test, p=<0.05).

Hypogonadism: Evaluable patients: 47. Twenty-four patients (51%) developed hypogonadism at a median of 2.2 years after HSCT. Ten-year cumulative risk of hypogonadism is 60.1% (SE=0.09). In univariate analysis, age at transplantation was the most important risk factor for hypogonadism (p<0.01): younger patients presented a lower incidence of hypogonadism (cut-off value 8.5 yrs, corresponding to the median age of the whole patients cohort, Table II). T-Student test confirmed this finding (p=0.01).

Pulmonary dysfunction: Evaluable patients: 46. Seven of them developed pulmonary disease (17.4%), at a median of 4 years after HSCT. Six patients showed restrictive (4 mild, 2 severe), 1 obstructive disease. Ten-year cumulative risk of pulmonary function abnormalities at 10 years is 15.7% (SE=0.06).

Cataract: Evaluable patients: 50. Thirty-six patients (72%) developed any form of cataract at a median time of 4.6 years after HSCT. Seven children (14%) developed severe cataract requiring surgery. Cumulative risk of severe cataract is 16% (SE = 0.06). At

Table 2. Univariate analysis. Freq: frequency; n: evaluable patients.

		Severe GH deficiency (n=50)		Hypothyroidism (n=47)		Hypogonadism (n=47)		Lung toxicity (n=46)		Cataract (n=50)	
		Freq	p	Freq	p	Freq	p	Freq	p	Freq	p
Age at HSCT	<8.5yrs	9/27	0.11	5/26	0.73	6/24	<0.01	4/24	1	22/27	0.10
	>8.5yrs	3/23		5/21		18/23		4/22		14/23	
Sex	Female	6/19	0.49	4/19	1	9/17	0.54	2/15	1	12/19	0.27
	Male	6/31		6/28		15/30		6/31		24/31	
Diagnosis	ALL	9/31	0.77	9/29	0.13	14/30	0.37	5/29	0.65	23/31	0.73
	AML	3/15		1/14		8/14		1/12		10/15	
Disease status at HSCT	CR1	3/21	0.2	2/19	0.17	10/18	0.43	2/19	0.44	14/20	0.79
	Other	9/29		8/28		14/29		6/27		22/30	
Type of HSCT	Autologous	2/19	0.1	2/17	0.29	11/19	0.32	1/17	0.22	10/19	0.02
	Allogeneic	10/31		8/30		13/28		7/29		26/31	
Chronic GvHD	No	5/18	0.7	3/18	0.21	7/15	0.64	2/16	0.19	13/18	0.06
	Yes	5/13		5/12		6/13		5/13		13/13	

univariate analysis, the most important risk factor is allogeneic transplantation (p = 0.02).

Secondary malignancies: Evaluable patients: 51. We observed 3 second cancers (5.9%), represented by 3 thyroid carcinomas: 2 follicular, 1 papillary. Cumulative risk of second malignancies at 10 years is 10% (SE = 0.07).

Discussion

In this study cohort of very long term survivors, cumulative incidences of late toxic effects are overall in the range of previously reported series [1, 2, 4, 5, 7–10, 12, 16, 18]. TBI was certainly not the only determinant of such a significant finding, since other factors (for example age at transplantation, graft-versus-host disease) did really play a role; due to the low numbers, it is not possible to make a comparison between different TBI fractionation schedules. As previously shown [14], we confirm that long-term survivors who underwent TBI and HSCT in childhood are at significant risk for developing late toxic effects, mainly within the endocrine system, and therefore should be strictly monitored during their follow-up in a multi-disciplinary setting for a long time-interval. On regards of future perspectives, probably new conditioning regimens TBI-free and innovative radiotherapy planning and delivery modalities [13] (e.g. Total Marrow Irradiation with Tomotherapy) will have an impact on reduction of incidence and severity of late toxic effects.

References

1. Belkacemi Y, Labopin M, Vernant JP, et al. Cataracts after total body irradiation and bone marrow transplantation in patients with acute leukaemia in complete remission: a study of the European Group For Blood and Marrow Transplantation. Int J Radiat Oncol Biol Phys 1998;41:459–468.
2. Berger C, Le-Gallo B, Donadieu J, Richard O, Devergie A, Galambrun C, et al. Late thyroid toxicity in 153 long-term survivors of allogeneic bone marrow transplantation for acute lymphoblastic leukaemia. Bone Marrow Transplant 2005;35:991–995.
3. Bölling T, Könemann S, Ernst I, Willich N. Late effects of radiotherapy to the thorax in children: a review of the literature. Strahlenther Onkol 2008;184:289–295.
4. Chou RH, Garrett BW, Kramer JH, Wara DW, Matthay KK, Crittenden MR, Swift PS, Cowan MJ, Wara WM. Toxicities of Total Body Irradiation for pediatric bone marrow transplantation. Int J Rad Oncol Biol Phys 1996;34: 843–851.
5. Cohen A, Rovelli A, Bakker B et al. Final height of patients who underwent bone marrow transplantation for haematological disorders during childhood: a study by the Working Party for Late Effects- EHSCT. Blood 1999;93:4109–4115.
6. Dörr W, Herrmann T. Second Tumors after Oncologic Treatment. Strahlenther Onkol 2008;184:67–72.
7. Faraci M, Barra S, Cohen A, Lanino E, Grisolia F, Miano M, et al. Very late nonfatal consequences of fractionated TBI in children undergoing bone marrow transplant. Int J Radiat Oncol Biol Phys 2005;63:1568–1575.
8. Ferry C, Gemayel G, Rocha V, et al. Long-term outcomes after allogeneic stem cells transplantation for children with haematological malignancies. Bone Marrow Transplant 2007;40:219–224.
9. Hoffmeister PA, Madtes DK, Storer BE, Sandres JE. Pulmonary function in long-term survivors of pediatric hematopoietic cell transplantation. Pediatr Blood Cancer 2006;47:594–606.
10. Kolb HJ, Socié G, Duell T, Van Lint MT, Tichelli A, Apperley JF, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. Ann Intern Med 1999;131:738–744.
11. Ljungman P, Urbano-Ispizua A, Cavazzana-Calvo M, Demirer T, Dini G, Einsele H, Gratwohl A, Madrigal A, Niederwieser D, Passweg J, Rocha V, Saccardi R, Schouten H, Schmitz N, Socie G, Sureda A, Apperley J, European Group for Blood and Marrow. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe. Bone Marrow Transplant 2006;37: 439–449.

12. Mertens AC, Ramsay NK, Kouris S, Neglia JP. Patterns of gonadal dysfunction following bone marrow transplantation. Bone Marrow Transplant 1998;22:345–350.
13. Ramm U, Licher J, Moog J, Scherf C, Kara E, Böttcher HD, Rödel C, Mose S. In vivo dosimetry with semiconducting diodes for dose verification in total-body irradiation. A 10-year experience. Strahlenther Onkol 2008;184: 376–380.
14. Rizzo JD, Wingard JR, Tichelli A, Lee SJ, Van Lint MT, Burns LJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and the American Society for Blood and Marrow Transplantation (EHSCT/CIHSCTR/ASHSCT). Bone Marrow Transplant 2006;37:249–261.
15. Schneider RA, Schultze J, Jensen JM, Hebbinghaus D, Galalae R, Kimmig BN. 20 years of experience in static intensity-modulated total-body irradiation and lung toxicity. Results in 257 consecutive patients. Strahlenther Onkol 2007;183:545–551.
16. Shalitin S, Phillip M, Stein J, Goshen Y, Carmi D, Yaniv I. Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence. Bone Marrow Transplant 2006;37:1109–1117.
17. Shank B, Hoppe RT. Radiotherapeutic principles of hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum FR, eds. Thomas Hematopoietic Cell Transplantation, 3rd ed., Blackwell Publishing Ltd: Malden, MA, 2004:178–197.
18. Socié G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol 2000;18:348–357.
19. Storb R. History of pediatric stem cell transplantation. Pediatr Transplant 2004;8(Suppl 5):5–11.

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