Growth, endocrine function and quality of life after haematopoietic stem cell transplantation

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Long term consequences of allogeneic haematopoietic stem cell transplantation during childhood: results of a cross-sectional single-centre evaluation

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Introduction

Over the past 35 years, haematopoietic stem cell transplantation (HCT) has become an important treatment modality for a wide range of life-threatening haematological and immunological disorders in both children and adults. Successful engraftment of allogeneic haematopoietic stem cells, however, will not occur in the presence of a competent immune system. Therefore, most recipients will have to be 'conditioned' for HCT. Moreover, when HCT is done to cure a haematological malignancy, intensive conditioning is needed, eradicating most of the host's haematopoiesis. The latter conditioning is qualified as myeloablative and is mostly effectuated with high dose chemotherapy, often combined with total-body irradiation (TBI). Such aggressive conditioning regimens will have their impact on the integrity of many other tissues as well. With an increasing number of long-term survivors, the late effects of HCT have become perceptible more distinctly, and ways to prevent them more imperative.
As one of the first centres in the world to perform a successful allogeneic bone marrow transplantation [1], the Leiden University Medical Centre (LUMC) has a large experience in HCT in children. Unfortunately many of our patients from the early days of HCT were lost to follow-up after reaching adulthood. We therefore decided to trace and recall as many long-term survivors as possible and evaluate the late effects of HCT in these patients.

Patients and Methods

Patient selection

We included all patients who received a HCT between 1974 and 1995 for either a haematological malignancy or severe aplastic anaemia (SAA) before the age of 18 years, who had a disease-free survival of at least 5 years and were at least 16 years of age at the time of the study. Patients living abroad were excluded, as well as one patient who would be unable to participate due to severe impairment caused by a massive intra-cranial haemorrhage in the period of HCT. A total of 33 of the 49 patients responded to our invitation, of whom 22 gave their informed consent. The main reasons for not participating

were: patients attending another hospital for their regular check-ups, the time-consuming nature of the study, and the study being regarded as too physically and emotionally taxing. Patient characteristics are presented in table 1.

Table 1. Patient Characteristics

Patient nr.	Sex (m/f)	Indication for HCT	TBI dose (Gy)	Age HCT (years)	Age study (years)	Follow up (years)	Remarks
1	m	SAA	-	10.2	31.0	20.8	
2	m	SAA	-	12.4	31.6	19.2	
3	m	SAA	-	15.1	32.2	17.2	
4	f	SAA PNH	4.0	17.9	27.8	10.0	
5	m	ALL 1	6.0 x 2	13.9	21.1	7.2	
6	f	ALL 1	6.0 x 2	15.7	21.8	6.0	
7	m	ALL 2	7.5	4.1	18.4	14.4	Cranial irradiation before HCT
8	m	ALL 2	7.5	5.8	19.6	13.8	Cranial irradiation before HCT
9	f	ALL 2	6.0 x 2	11.9	18.1	6.1	
10	f	ALL 2	8.0	14.3	29.3	15.1	Cranial irradiation before HCT
11	f	JMML	5.0	0.9	19.2	18.4	
12	f	AML	7.5	7.0	25.8	18.8	Papillary thyroid carcinoma
13	m	AML	7.5	7.4	21.6	14.3	
14	f	AML	8.0	10.7	24.8	14.1	
15	f	AML	8.0	10.1	24.3	14.2	
16	f	AML	8.0	14.3	30.3	16.0	2 x spontaneous abortion
17	f	AML	8.0	15.9	25.2	9.3	
18	f	AML	8.0	15.2	31.3	16.1	
19	m	AML	8.0	10.3	21.1	10.8	HCT twice, progressive lung disease, avascular hip necrosis
20	m	MDS	7.5	9.6	23.5	13.9	
21	f	CML (Ph+)	7.5	10.0	27.6	17.8	Avascular hip necrosis
22	m	NHL 2	6.0 x 2	14.1	20.7	6.6	

SAA	Severe Aplastic Anaemia
SAA PNH	Severe Aplastic Anaemia Paroxysmal Nocturnal Haemoglobinuria
ALL1	Acute Lymphoblastic Leukaemia in 1st remission
ALL 2	Acute Lymphoblastic Leukaemia in 2nd remission
JMML	Juvenile MyeloMonocytic Leukaemia
AML	Acute Myelogenous Leukaemia in 1st remission
CML (Ph+)	Chronic Myelogenous Leukaemia (Philadelphia positive)
NHL 2	Non-Hodgkin Lymphoma in 2nd remission

Conditioning for HCT

Conditioning consisted of cyclophosphamide (Cy, 60 mg/kg/day i.v. for 2 consecutive days) in all patients and was combined with TBI in children suffering from a haematological malignancy. In addition to this Cy-TBI regimen, cytarabine (1 g/m2/day for 2 consecutive days) was given to patients treated for myeloid leukaemia or myelodysplastic syndromes between 1988 and 1998 (n=1). From 1990 onward, patients treated for lymphoblastic leukaemia or non-Hodgkin lymphoma received etoposide (350 mg/m2/day for 2 consecutive days) (n=4) in addition to TBI-Cy. TBI was administered unfractionated (i.e. as one or two single fractions > 4.0 Gy), delivered at a mean dose rate of 23 cGy/min. To reduce radiation damage, lungs were compensated for their different radiation-density, and eyes were shielded during TBI from 1987 onward.

As age is an important determinant with respect to tolerability of irradiation dose in children, a TBI regimen with age-dependent total dose was applied, i.e. 0-2 years: 5.0 Gy, 2-4 years: 7.0 Gy, 4-10 years: 7.5 Gy, >10 years 8.0 Gy. The latter dose was 'increased' in 1989 to 2 single fractions of 6.0 Gy, given on 2 consecutive days, instead of the equivalent 9.0 Gy once, which had too much side effect in adults. Of the 4 patients treated for SAA, one who was transfusion-sensitised received 4 Gy TBI in addition to Cy, the other 3 received no TBI.

Growth and endocrine functions

Parameters used to evaluate growth and endocrine function were height, weight, serum levels of insulin-like growth factor 1 (IGF-1), free thyroxin (FT4), thyroid stimulating hormone (TSH), luteinising hormone (LH), follicle stimulating hormone (FSH), oestradiol, testosterone, 25-OH vitamin D, use of hormone preparations (e.g. thyroxine, oral contraception etc.) and bone mineral density (BMD). Height is measured with a stadiometer and expressed in standard deviation score (SDS) for age and sex based on Dutch references [2]. Target height was calculated from parental height with corrections for secular trend (+4.5 cm) and sex differences (13 cm) [2]. Final height (FH) SDS was compared to height SDS at the time of HCT and to target height SDS. BMD was measured with dual-emission x-ray absorption (DEXA) scan (Hologic QDR) in femoral necks and lumbar spine and results were expressed as gender specific

SD scores for young adults. Osteoporosis was defined as BMD <-2.5 SDS, Osteopenia as BMD < -1.0 SDS.

Renal function

Creatinine clearance was estimated using the formula of Cockcroft and Gault [3] with correction for body surface area. Glomerular Filtration Rate (GFR) was estimated using the Modification of Diet in Renal Disease Study 1 (MDRD1) formula, which includes age, sex, serum creatinine, serum urea and serum albumin [4]. GFR and creatinine clearance were considered normal if > 85 ml/min/1.73m^2.

Lung function

We used a standardised questionnaire to evaluate subjective pulmonary symptoms. Parameters for lung function were forced expiratory volume in one second (FEV1), functional residual capacity (FRC), vital capacity (VC), total lung capacity (TLC), residual volume (RV), and transfer factor for carbon monoxide (T_{LCO}), corrected for haemoglobin content. Results are expressed as percentage of the predicted values, derived from Quanjer et al. for VC, FEV1 [5], from Stocks et al. for TLC, FRC and RV [6], and from Stam et al. for T_{LCO} [7].

Other late effects

An ophthalmologist and a dermatologist examined patients for dermal and ocular late effects. Secondary tumours were identified from the medical records.

All laboratory evaluations were performed using standard in house, commercially available assays.

Quality of life

The sickness impact profile and the Medical Outcome Study 36-item Short Form Health Survey were used as generic questionnaires in the assessment of Quality of life (QOL). The Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale (FACT-BMT) was used as a disease-specific measure of QOL. Coping was assessed by means of the Utrecht coping list.

Results

Table 2 summarises the results of individual patients.

Growth and endocrine function

All patients had reached FH. In seven patients, pubertal growth spurt was almost completed at time of HCT (including one 12 year old boy with SAA who had received high doses of androgens for several years; his height at HCT was 186.5 cm). Of the remaining 15 patients, two had received cranial irradiation prior to TBI. Their FH's were –4.0 and –3.3 SDS. One other patient (no TBI) had received high doses of corticosteroids for several years, first for his SAA, later for severe chronic graft-versus-host-disease (GVHD). His FH was –3.5 SDS. In the remaining 12 patients, only one patient (not treated with TBI) had an increase in height SDS (+1.4 SD) between HCT and FH. In the other 11 patients (all had received TBI) median FH SDS was –2.1 (range -3.7 to 0), median difference between height SDS at HCT and FH SDS was - 1.6 (range –2.3 to –0.1), and median difference between target height SDS and FH SDS was –1.6 (range –2.6 to –0.5). None of the patients had been treated with growth hormone (GH).

Hypergonadotrophic hypogonadism was diagnosed in 10 of the 12 girls, with recovery of gonadal function in two of them. Six girls received sex hormone replacement therapy and two used oral contraception. One patient who had recovered from hypogonadism had 2 pregnancies, both resulting in spontaneous abortion. All 7 males treated with TBI and 1 of the 3 males who only received cyclophosphamide had elevated FSH levels, suggestive of severely decreased fertility. Three boys were using sex hormone replacement therapy. In one of the remaining 7 boys testosterone was decreased and LH elevated, suggestive of decreased Leydig cell function.

One patient with pre-existing hyperthyroidism before HCT underwent thyroidectomy and received thyroxine suppletion. Of the remaining patients, two had developed primary hypothyroidism after TBI and were receiving thyroxine suppletion. Free T4 and TSH were normal in all patients.

None of the patients had vitamin D deficiency. In two patients (one male), BMD measurement of the femoral neck was impossible due to hip replacement surgery after avascular hip necrosis as a result of extensive use of glucocorticosteroids for GVHD. One female patient had osteoporosis of the

lumbar spine BMD (BMD –2.6 SDS), with osteopenia of both femoral necks (-1.8 and –2.0 SDS). Another female patient had osteoporosis of her right femoral neck (BMD –2.6 SDS), with osteopenia of the other hip and lumbar spine (BMD –2.4 and –1.9 SDS respectively). Of the remaining patients, 9/18 had osteopenia of one or both hips, and 6/20 had osteopenia of the lumbar spine.

Renal function

Median estimated creatinine clearance was 100 ml/min/1.73m^2 (range 83-124). Median estimated GFR using the MDRD1 formula was 99 ml/min/1.73m^2 (range 76-131). One patient had a decreased estimated creatinine clearance (83 ml/min/1.73m^2) but normal estimated GFR (88 ml/min/1.73m^2). Another patient had a decreased estimated GFR (76 ml/min/1.73m^2) but normal estimated creatinine clearance (89 ml/min/1.73m^2). In both patients actual creatinine clearance (measured using 24-hr urine samples) was normal (101 and 141 ml/min/1.73m^2 respectively).

Lung function

Apart from the patient with severe pulmonary fibrosis after a re-transplantation, 3 patients reported mild shortness of breath during exercise. The remaining 18 patients were free of pulmonary symptoms. Lung function tests were missing in one female patient due to a technical error. One patient had severe pulmonary fibrosis due to radiation damage and pulmonary GVHD, which resulted in oxygen dependency and a VC of only 20% of predicted. This patient was excluded from the analyses. Median VC was 80% (54-115), median TLC was 83% (56-125), median RV was 70% (42-222) median RV/TLC was 92% (56-158), median FEV1/VC was 106% (88-124) and median T_{LCO} was 60% (40-104). TLC, VC and T_{LCO} were significantly decreased in our population (one-sample Student t-test, $p<0.001$), whereas FEV1/VC was significantly increased ($p=0.015$). All patients with pulmonary symptoms had abnormal pulmonary function tests.

Other late effects

Of the 19 TBI treated patients, 12 received TBI before 1987, which means that they did not have their eyes shielded to reduce the radiation dose to the

lenses. Two of these patients had a history of lens extraction for severe cataract after HCT. In the other 10 patients, mild cataract was found. The one patient who received a relatively low dose of 4 Gy TBI also had mild cataract. She had also received high doses of corticosteroids during the initial treatment of her SAA. Of the 7 patients receiving TBI after 1987 (i.e. with eye shielding), only one had very mild cataract. Of the 3 patients who did not receive TBI, one patient, treated with corticosteroids for GVHD for a long time, had mild cataract. Two patients with chronic GvHD had keratoconjunctivitis sicca.

Physical examination by a dermatologist revealed no dysplastic naevi in any of the patients. One patient was treated for basal cell carcinoma in the past, and in one patient a basal cell carcinoma was diagnosed and excised. Four patients had sclerotic skin lesions as a result of chronic GVHD.

Three patients (all treated with TBI) had developed a secondary tumour (one thyroid carcinoma and 2 basal cell carcinoma, as described above).

Quality of life

Results of the QOL measurements are published elsewhere [8]. Of the generic QOL measures, most results fell within the normal range of functioning, although some illness-related impairment was reported on subscales for general and work-related functioning. Compared to a reference sample of patients who had received BMT as adults, patients involved in this study scored significantly higher on the ‘emotional well-being’ subscale of the FACT-BMT, indicating significantly better emotional functioning. The age at BMT and total body irradiation (TBI) were not related to patients’ QOL.

Table 2. Late effects in individual patients

Pat. No.	Sex (m/f)	Indication HCT	TBI dose (Gy)	FH (SDS)	FH-TH (SDS)	Gonadal dysfunction	Hypo-thyroidism	BMD	Renal function	Lung function	Cataract	GVHD	2nd tumour
1	m	SAA	0	***	*			*	*		*	**	
2	m	SAA	0		*			*		*	*	**	
3	m	SAA	0			*							skin
4	f	SAA	4.0		*	*		*		*	*		
5	m	ALL 1	6.0 x 2			*		*					
6	F	ALL 1	6.0 x 2	*		*		**					
7	m	ALL 2	7.5	***	***	*		*			*		
8	m	ALL 2	7.5	***	***	*	*	*		*	*	*	
9	f	ALL 2	6.0 x 2			*							
10	f	ALL 2	8.0	*		*		*		*	*	**	thyroid
11	f	JMML	5.0	**	**						*		
12	f	AML	7.5	**	**		*			*	**		
13	m	AML	7.5	***	**	*				*	*		
14	f	AML	8.0	**	*	(*)		*		*	*		
15	f	AML	8.0	*	*	*				*	*		
16	f	AML	8.0			(*)		*		*	*		
17	f	AML	8.0	**	*	*				*			
18	f	AML	8.0			*		*	*	missing	**		skin
19	m	AML	8.0	*	**	*		*		**	*		
20	m	MDS	7.5	***	**	*		*		*	*		
21	f	CML Ph^+	7.5	**	*	*		**		*	*	*	
22	m	NHL	6.0 x 2		*	*		*		*	*		
				* <-1 sd ** < -2 sd *** <-3 sd		* hypogonadism (*) recovered		* osteopenia ** osteoporosis	* < 85 ml/min/ 1.73m^2 ** <50%	* < 75%	* mild ** severe	* limited ** extended	

Discussion

Impaired growth is an important late complication of HCT, with TBI as the most important etiological factor. TBI may have a direct effect on growth (by inducing growth plate damage) as well as an indirect effect (by causing GH deficiency, hypogonadism or hypothyroidism). The indirect effects can be overcome by hormone replacement therapy. Other factors that may contribute to impaired growth are chronic GVHD, its treatment with glucocorticosteroids, and cranial irradiation prior to HCT, resulting in GH deficiency.

In our evaluation, median adult height after TBI was 1.6 SDS (±11 cm) lower compared to both target height and height at HCT. In patients who also had received cranial irradiation, adult height was even more compromised. These results are comparable to final heights reported in the literature [9-12].

Except for the two girls who were the youngest at the time of HCT, all women who had received TBI developed hypergonadotrophic hypogonadism after TBI. In two of these women gonadal function recovered, and one of them became pregnant twice. These results are in line with the literature, reporting a positive correlation between age at HCT and incidence of ovarian failure [13-15]. As could be expected from earlier reports [16], TBI resulted in decreased fertility in men. In addition, with increasing age, signs of Leydig cell failure became more evident, with elevated serum levels of LH in 4 of 7 men.

Hypothyroidism after HCT is related to radiation damage to the thyroid gland. The incidence of hypothyroidism after TBI in this study was 2/18 (11%) which is relatively low compared to incidences reported in the literature (45% after sf-TBI and 15% after fractionated TBI) [16]. An explanation for this lower incidence could be the relatively low total TBI dose in our study (most patients received 7.5-8.0 Gy, compared to 10 Gy in most studies with sf-TBI).

Osteopenia was present in 64% of the patients, two of whom also had osteoporosis. As most patients had a relatively low adult height, BMD SDS is probably slightly higher if corrected for height. Unfortunately, these data were not available. The percentage of patients with reduced BMD in our study is comparable to that reported in adults by Kauppila et al. (68%) [17]. The most important factor contributing to the decreased BMD is the use of glucocorticosteroids in patients with chronic GVHD. In addition, hypogonadism (especially in girls with ovarian failure), non-compliance in patients with sex

hormone replacement therapy, and TBI also contribute to the decreased BMD [16]. The small population size prevented further analyses of these influencing factors.

Renal function was normal in all 22 patients. Decreased renal function is related to the use of nephrotoxic agents (e.g. cisplatin, cyclosporine, amphoterecin B) and total TBI dose. The reported incidence of renal dysfunction in adults receiving fractionated TBI at total doses of less than 12 Gy is approximately 5% [18;19]. Recently, results of a prospective study into chronic renal failure after HCT were reported by our transplant centre [20]. In that study, TBI was not a risk factor for either acute or chronic renal failure in the first 2 years after HCT. Frisk et al., however, report repeated measurements of GFR and describe a gradual decrease in GFR with time after HCT [21]. They report renal insufficiency (GFR < 70 ml/min/1.73m^2) in as much as 27% of 26 patients after paediatric HCT and 7.5 Gy single-fraction TBI (median follow-up of 10 years), compared to 0% of the 14 patients receiving radiation-free conditioning for HCT. We do not have an explanation for the low incidence of renal insufficiency after TBI in our patients, but differences in the use of nephrotoxic agents during treatment of initial disease and during the transplantation period may play a role.

There was a decrease in lung function parameters compatible with restrictive pulmonary disease in 66% of our population (i.e. decreased TLC and RV, increased FEV1/VC). In addition, diffusion capacity, measured by T_{LCO} was also significantly decreased (<80% of predicted) in 10/20 (50%) patients. None of the patients had obstructive lung disease. The majority of the patients (82%) were free of symptoms. Restrictive lung disease and decreased diffusion capacity is associated with TBI, and in longitudinal studies lung function stabilises after initial decrease [11;22-25]. In contrast to the high incidence of restrictive lung disease in our population, Frisk et al. reported an incidence of only 21% 10 years after 7.5 Gy sf-TBI [11] , and Cerveri et al. reported 26% two years after 6x2.0 Gy fractionated TBI [24]. These differences can be explained by the absence of GVHD in the first study (autologous transplants only) and the shorter follow-up and possibly the use of fractionated TBI in the latter study.

The incidence of cataract, a well known late effect of ocular irradiation, depends on total dose, dose rate and fractionation. Our results are comparable to those reported in the literature [26;27]. The study of Kempen-Harteveld et al. [27]

was a national study on paediatric HCT recipients and included all patients receiving TBI in our centre until 2001. Before eye shielding was applied, the incidence of cataract after sf-TBI was >90%, whereas with eye shielding it was approximately 30%.

Three patients had developed a secondary malignancy. Based on both animal data and the experience with radiation induced tumours in humans, more secondary tumours can be expected in the future. [28;29]

Our cross-sectional evaluation revealed a substantial number late of effects in a wide variety of organ systems, and all patients in our study suffered from more than one such late complication. Therefore life-long follow-up of all patients treated with HCT is indicated. Shielding of radiosensitive organs may reduce the incidence of late effects (e.g. eye-shielding to prevent cataract), but is not feasible for many organs (e.g. gonads) in children treated for malignancies. Growth hormone therapy is a promising option for the treatment of radiation induced growth impairment (own unpublished data), but multi-centre studies are needed to determine its benefits and risks in this category of patients.

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