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

Bakker, B.

GROWTH HORMONE (GH) SECRETION AND RESPONSE TO GH THERAPY AFTER TOTAL-BODY IRRADIATION AND HAEMATOPOIETIC STEM CELL TRANSPLANTATION DURING CHILDHOOD

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Bakker B[1], Oostdijk W[1], Geskus RB[2], Stokvis-Brantsma WH[1], Vossen JM[1], Wit JM[1]

[1] Department of Paediatrics, Leiden University Medical Centre, Leiden, The Netherlands
[2] Department of Medical Statistics, Leiden University Medical Centre, Leiden, The Netherlands

Abstract

Growth is often impaired in children receiving total-body irradiation (TBI) as conditioning for haematopoietic stem cell transplantation (SCT). Radiation damage to the growth plates is an important cause, but decreased growth hormone (GH) secretion may also play a role. In January 1997 we introduced a protocol for the treatment with GH of children with impaired growth after single-fraction TBI. This study is an evaluation of that protocol. The main outcome measure is the effect of GH therapy on height SDS after onset of GH therapy, estimated by random-effect modelling with corrections for sex, age at time of SCT and puberty (data analysed on intention-to-treat basis). Between January 1997 and July 2005, 66 patients (48 male) treated for haematological malignancies had at least two years of disease-free survival after TBI-based conditioning for SCT. Stimulated and/or spontaneous GH secretion was decreased in 8 of the 29 patients tested because of impaired growth. Treatment with GH (daily dose 1.3 mg/m2 body surface area) was offered to all 29 patients and initiated in 23 of them (17 male). At time of analysis, median duration of therapy was 3.2 years; median follow-up after start of GH therapy was 4.2 years. The estimated effect of GH therapy, modelled as non-linear (logit) curve, was +1.1 SD after 5 years. Response to GH therapy did not correlate to GH secretion status.

We conclude that GH therapy has a positive effect on height SDS after TBI, irrespective of GH secretion status.

Introduction

Growth impairment is a frequent complication in children receiving total-body irradiation (TBI)-based conditioning for haematopoietic stem cell transplantation (SCT), with a mean decrease in height SDS between pre-pubertal SCT and final height of approximately 1.0 to 1.5 SDS in most studies [1-5]. Radiation-induced damage to the epiphyseal growth plate is a major cause, but other factors can also attribute to impaired growth, e.g. radiation-induced hypothyroidism, hypogonadism or growth hormone deficiency (GHD). Several studies have shown that decrease in height SDS is greater in boys, in younger children and in children with a history of cranial irradiation (CI) or craniospinal irradiation (CSI) [2-6]. Studies on the effect of GH therapy on growth after TBI are limited and almost exclusively deal with children diagnosed as having GHD. We investigated the effect of GH therapy in children with impaired growth after TBI and SCT, irrespective of the diagnosis of GHD.

Materials and methods

In January 1997 we implemented a protocol for the diagnostic evaluation and subsequent treatment of children and adolescents (<16 years of age) with impaired growth after TBI-based conditioning for SCT. The treatment protocol was approved by the Patient Care Committee and Scientific Research Committee of the Department of Paediatrics of the Leiden University Medical Centre, and by the Review Board of the Netherlands' Organisation for Scientific Research (NWO). Informed consent was obtained from all patients involved in this study.

Inclusion criteria

1) TBI-based conditioning and SCT for a haematological malignancy before the age of 14 years *and 2)* at least two years relapse-free survival after SCT *and* 3) impaired growth (decrease in height SDS > 0.5 SD since SCT or height SDS below patient's target height range) *and* 4) absence of other causes of impaired growth (e.g. CI as part of initial treatment, chronic graft-versus-host

disease, pubertal delay, untreated hypothyroidism, prolonged use of corticosteroids).

Diagnostic evaluation

All patients eligible for inclusion were offered evaluation of GH secretion. Priming with sex steroids was used in prepubertal girls ≥ 8 years of age and prepubertal boys ≥ 9 years of age. The peak serum concentration of GH after stimulation with clonidine (0.15 mg/m^2 orally) or arginine (0.5 g/kg i.v.) was used as a measure of stimulated GH secretion. Spontaneous GH secretion was measured by nocturnal GH concentration profiles, using 12 h continuous blood withdrawal (2 ml/h) from 2000 h until 0800 h with a sample interval of 20 minutes. Results were analysed using the Cluster algorithm [7].

Assays and reference values

Serum GH was measured using a time-resolved immunofluorometric assay, specific for the 22-kD form of GH with detection limit 0.01 µg/l, (Delfia hGH IFMA; Wallac, Turku, Finland, calibrated against the international reference preparation 80/505 in which 2.6U=1mg). Plasma levels of IGF-I and IGFBP-3 were determined at the endocrine laboratory of the Wilhelmina's Children's Hospital, Utrecht, the Netherlands. The assays were described previously [8]. Results are expressed as age- and sex-specific SDS.

According to national criteria, peak GH > 20 mU/l after pharmacological stimulation was considered sufficient. Based on nation-wide harmonisation of GH assays, 13.8 mU/l in our assay corresponds to 20 mU/l in the national reference assay. Therefore, GH response was considered insufficient if peak GH was < 13.8 mU/l (5.3 ng/ml).

Criteria for normal spontaneous GH secretion were maximum GH > 5.3 µg/l and mean GH concentration > 1.2 µg/l, based on assay-specific references [9].

Growth hormone deficiency (GHD) was defined as an insufficient peak GH (spontaneous or stimulated) on 2 separate occasions. GH neurosecretory dysfunction (NSD) was defined as sufficient peak GH after pharmacological stimulation but decreased maximum peak GH or mean GH concentration in a 12 hour GH secretion profile.

Treatment and follow-up

After diagnostic evaluation of GH secretion status, all patients were offered treatment with recombinant human GH at a daily dose of 1.33 mg/m^2 body surface area.

Height, Tanner stages of breast or genital development [10] and testicular volume (measured with an orchidometer) were monitored at 3 months' intervals during treatment with GH. Height was measured with a Harpenden stadiometer and expressed as standard deviation scores (SDS) for sex and age [11]. Target height (TH) was calculated according to the formula introduced by Tanner et al [12] with corrections for sex (13 cm) and secular trend (4.5 cm), and TH range was defined as TH SDS +/- 1.3 SDS.

The onset of puberty was defined as the age at which breast development was first recorded in girls (Tanner breast stage ≥ B2) or a testicular volume ≥ 4 mL was reached in boys. If signs of pubertal development (e.g. penile growth and pubic hair development) had occurred in boys while testicular volume had not reached 4mL, onset of puberty was determined on the basis of the combination of progression of Tanner stages and increasing serum levels of testosterone. If puberty was induced, onset of puberty was defined as the start of sex hormone replacement therapy.

After completion of therapy, height was measured at 6 months' intervals until final height (patients were considered to have reached final height if growth was less than 1.0 cm over a period of more than 12 months after the age of 15 years).

Patient population

Between 1997 and 2005, 66 patients met the inclusion criteria (patient characteristics are summarised in table 1). Stimulated and spontaneous GH secretion were evaluated in 29 children, including one patient (nr. 29 in the tables, treated outside the protocol) who did not meet the inclusion criteria (SCT at age 14.3 years and <2 years survival). Twenty-three children started GH therapy (effective mean starting dose 34 µg/kg/day, range 27-39). For two of these patients (nr. 27 and 28), evaluation of GH secretion as well as follow-up of GH therapy took place in another centre, with a different GH assay and a lower starting dose of GH in one (0.67 mg/m^2; corresponding to 18 µg/kg/day).

Table 1. Patient characteristics.
Figures represent either absolute numbers, or medians with ranges in parenthesis.

	All patients (n=66)	GH tested (n=29)	GH treated (n=23)
Male : female	48 : 18	22 : 7	17 : 6
Age HCT	7.7 (1.7-14.3)	7.7 (1.7-14.3)	7.7 (1.7-14.3)
Age GH evaluation	-	12.5 (7.2-15.9)	12.2 (7.2-15.9)
Age last visit	16.6 (8.8-22.4)	16.8 (9.2-19.3)	17.3 (10.8-19.3)
Follow-up since HCT	7.7 (2.0-17.0)	8.1 (2.1-17.0)	9.1 (2.1-17.0)
Follow-up since GH evaluation	-	4.4 (0.0-7.8)	5.1 (0.6-7.8)
Follow-up since start GH	-	-	4.2 (0.5-7.7)
Indication HCT			
ALL 1st	10	6	4
ALL 2nd	27	13	12
AML 1st	11	6	6
AML 2nd	4	1	-
MDS	8	3	1
CML	4	-	-
NHL 2nd	2	-	-
Type of graft			
Allogeneic	60	28	22
Autologous	6	1	1
TBI dose			
5.0 Gy	1	-	-
7.0 Gy	9	5	5
7.5 Gy	37	15	12
8.0 Gy	2	1	-
2 x 6.0 Gy	17	8	6
Testicular Booster	6	4	3

Conditioning for SCT

Conditioning for SCT consisted of TBI and cyclophosphamide (60 mg/kg/day i.v. for 2 consecutive days) in all patients. In addition, 19 patients also received cytarabine (1 g/m^2/day for 2 consecutive days) and 37 patients received etoposide (350 mg/m^2/day for 2 consecutive days). All patients received unfractionated TBI, delivered at a mean instantaneous dose rate of 25 cGy/min. As age is an important determinant of the tolerable total irradiation

dose in children, a TBI regimen with age-dependent total dose was applied (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 many side effects in adults). Six boys treated for ALL received additional prophylactic testicular irradiation (10 Gy in 4 fractions prior to TBI).

Statistical Analyses

S-PLUS 6 Professional (Insightful corp., Seattle WA, USA) was used for all statistical analyses, with significance level set at 5%. We recently developed sex-specific models that describe the changes in height SDS with time after TBI and SCT, with corrections for the effects of individual puberty and for the effect of puberty in the reference population, using the function 'lme' (linear mixed-effects) in S-PLUS [6]. These models are based on 75 children who had at least 2 years of follow-up after pre-pubertal TBI-based conditioning for SCT for a haematological malignancy. Three of the 23 GH treated children from the present study were not included in this previous study (nrs. 5 and 14 were not pre-pubertal at time of SCT, nr. 29 due to relapse), the others contributed to the initial models until the start of their GH therapy.

For the present analyses, we added the height measurements taken after start of GH therapy of these 20 patients to the dataset (total set 1236 post-TBI height measurements of 75 patients) and subtracted the *individual* growth profiles (obtained from the model) from the individual height SDS after start of GH therapy. The resulting values describe the difference between *individually* predicted growth (i.e. without GH therapy) and actual growth after start of GH therapy. This estimated effect of GH therapy was then analysed by adding a variable 'time since start GH therapy' to the model with a non-linear (logit) effect. To prevent possible selection bias by exclusion of patients who discontinued therapy due to a poor response, analyses of the effect of treatment were done on an intention-to-treat basis. Therefore all data obtained after start of therapy was included in the analyses, even if GH therapy was discontinued by that time.

Table 2. Results of the evaluation of GH secretion status in 29 patients with impaired growth after HCT. Patients 27 and 28 were tested in another centre; patient 29 was treated outside the protocol (< 2 years disease free survival at time of evaluation)

				Spontaneous GH secretion		Spontaneous GH secretion					
Patient	sex	Age GH Evaluation	Tanner stage	Mean GH (µg/l)	Peak GH (µg/l)	Peak 1 GH (µg/l)	Peak 2 GH (µg/l)	IGF-1 (SDS)	IGFBP-3 (SDS)	Diagnosis	GHRx
1	M	13.3	1	0.4	1.9	3.6	4.1	-1.8	-1.8	GHD	yes
2	M	14.3	2	0.5	3.8	7.8		-1.3	0.5	GHNSD	yes
3	M	8.8	1	0.6	3.1	4.8		-0.6	1.0	GHNSD	no
4	M	13.3	2	0.9	3.7	5.0	5.5	-1.9	-1.1	GHNSD	yes
5	M	14.2	2	-	-	0.7	4.5	-0.5	-1.7	GHD	yes
6	M	14.1	3	1.0	7.7	12.6	21.7	1.8	0.7	GHNSD	no
7	M	11.1	1	1.3	4.4	8.4		-1.5	0.8	normal	yes
8	M	7.2	1	1.4	8.0	17.8		-1.0	-2.0	normal	yes
9	F	11.9	2	1.5	7.3	4.2		0.2	1.0	Normal	no
10	M	9.7	1	1.7	9.9	11.7		-0.7	0.8	normal	yes
11	F	12.5	1	1.9	9.2	5.9	8.1	-1.7	0.7	normal	yes
12	M	12.8	1	2.0	12.2	12.4		-0.9	0.0	normal	yes
13	M	13.2	3	2.0	10.6	8.3		0.4	1.4	normal	no
14	F	15.1	3	2.0	6.1	15.5		-2.3	-0.9	normal	yes
15	M	7.4	1	2.0	11.2	12.4		0.6	-0.4	normal	yes
16	F	7.6	1	2.1	11.0	7.0	5.1	1.3	2.4	normal	yes
17	M	12.6	2	2.1	13.3	19.3	11.5	-0.8	1.1	normal	yes
18	F	14.1	4	2.3	9.2	3.8	15.9	-1.0	-0.3	normal	yes
19	M	12.1	2	2.4	15.0	8.0		-0.4	1.0	normal	yes
20	M	11.3	1	2.4	13.3	9.4		0.5	0.9	normal	yes
21	M	12.2	2	2.5	13.3	9.6	2.2	-0.5	0.9	normal	yes
22	F	12.9	3	2.7	23.3	12.2		0.2	1.2	normal	yes
23	F	10.3	1	2.9	8.7	18.5	10.2	-1.8	-0.1	normal	yes
24	M	11.2	2	2.9	10.2	7.9		0.4	1.2	normal	yes
25	M	15.2	4	3.6	27.3	11.4		-1.3	0.4	normal	no
26	M	12.9	3	6.2	21.7	24.3		0.0	2.0	normal	no
27	M	10.7	1	4.3	-	25.8	7.7	-2.1	-0.8	normal	yes
28	M	9.9	1	1.6	-	24.	0.8	-2.7	-1.0	GHNSD	yes
29	M	15.9	2	0.9	5.8	7.1	4.6	-3.3	1.2	GHNSD	yes
		Reference median (range):		2.2 (1.2 – 7.9)	10.5 (5.1- 36.5)						

Results

Growth hormone secretion

Results of the analyses of GH secretion are represented in table 2. GH secretion was impaired in 7 of the 27 children tested in our clinic, including the patient treated outside the protocol. Two patients had classical GHD, five had NSD. Of the two patients tested in another centre (27 and 28), one had a decreased integrated mean spontaneous GH secretion using assay-specific reference values for that centre [13].

Effect of GH therapy

Table 3 summarises height SDS at different time points in the children receiving GH therapy. The median duration of GH therapy was 3.2 years (range 0.1-7.3 years).

Table 3. Target height SDS and height SDS at different time-points in the 23 patients treated with GH. ***** Adult height: Final height expressed as SDS for age 21 years.

Patient	Sex	Duration GH Rx (years)	follow up since start GH (years)	Target height (SDS)	Height at SCT (SDS)	Height at start GH (SDS)	Delta height after start GH (SDS)	Adult height* (SDS)
1	m	1.5	1.5	-1.7	-2.3	-3.5	0.1	
2	m	1.9	4.0	1.1	1.2	0.1	0.0	-0.1
4	m	3.3	4.1	1.6	-0.3	-0.9	0.5	
5	m	2.1	2.6	-2.2	-0.6	-2.6	0.0	
7	m	4.0	4.0	-0.3	-0.5	-1.6	-0.3	
8	m	7.2	7.2	0.0	0.4	-0.4	0.6	
10	m	6.4	6.4	-0.7	-2.7	-2.4	0.2	
11	f	3.6	5.4	0.6	-0.2	-1.0	1.0	-0.1
12	m	2.6	4.7	-0.2	-1.0	-1.8	-0.6	-2.7
14	f	0.1	2.5	-0.3	-1.5	-2.0	0.1	-2.0
15	m	3.1	3.1	0.6	-1.2	-1.7	1.1	
16	f	5.7	6.3	1.0	-2.2	-2.0	0.4	
17	m	3.1	6.4	1.1	-0.9	-1.2	-0.8	-2.4
18	f	1.6	3.6	0.0	-0.7	-1.5	0.2	-1.4
19	m	3.0	5.8	1.6	1.2	0.2	0.4	0.4
20	m	2.3	2.3	1.1	-1.1	-1.5	0.1	
21	m	3.3	3.3	-0.1	-1.5	-1.4	0.2	
22	f	0.7	4.2	0.7	-0.7	-1.7	0.2	-1.6
23	f	4.9	7.7	0.2	-1.0	-3.4	0.4	-3.2
24	m	4.3	5.3	1.2	-0.5	-0.3	-0.4	-1.7
27	m	3.8	4.2	-1.4	-3.0	-3.5	-0.2	-4.0
28	m	5.3	5.3	0.4	0.6	-0.8	0.3	
29	m	0.7	0.7	-0.8	-1.1	-1.6	0.3	

Figure 1 represents the relative changes in height SDS in the 23 children treated with GH compared to height SDS at start of GH therapy. In the first year of therapy, there was a mean change in height of +0.35 SDS/year. Two patients discontinued therapy and one patient (nr 29, treated outside the protocol) died 27 months after SCT after relapse of his initial disease. In 17 of the remaining 20 children, there was an increase in height SDS in the first year of therapy, whereas in 3 there was a slight decrease (<0.05 SDS/year).

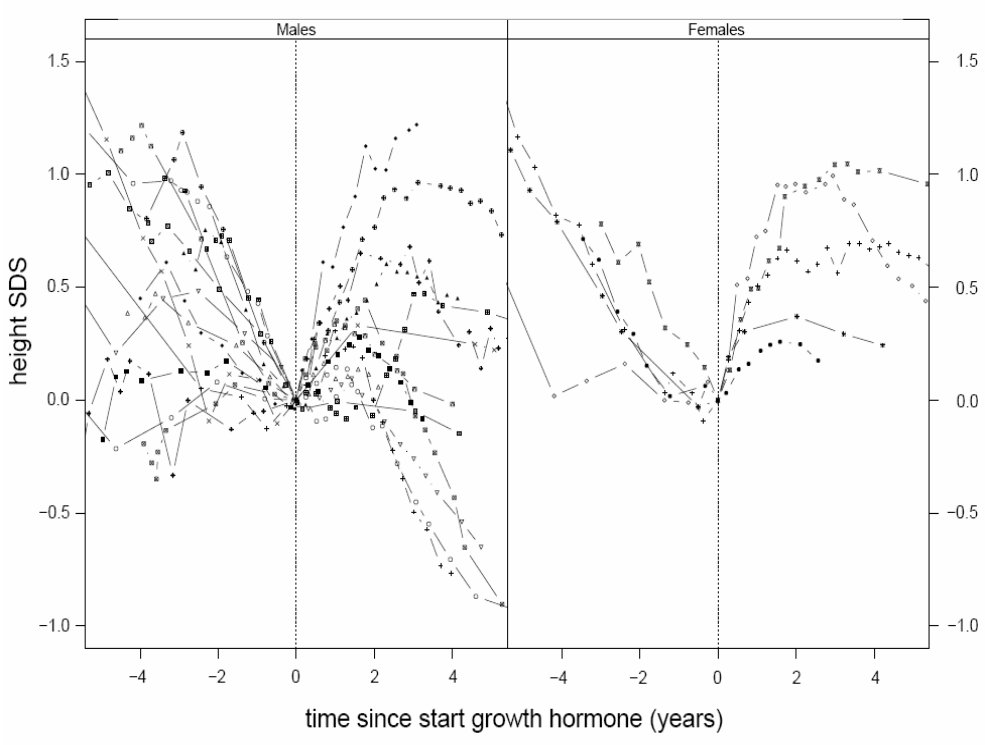

Figure 1. Changes in height SDS after start of GH therapy in the 23 GH-treated children. The x-axis represents time since start of GH therapy in years, the y-axis height SDS compared with height SDS at start of GH therapy. Left panel: males, right panel females.

The estimated net effect of GH therapy in the 20 patients who received SCT before the onset of puberty is represented in figure 2. The estimated net effect after 5 years of therapy is 1.14 (CI 0.88-1.41) SDS, with no significant difference between sexes (p=0.565).

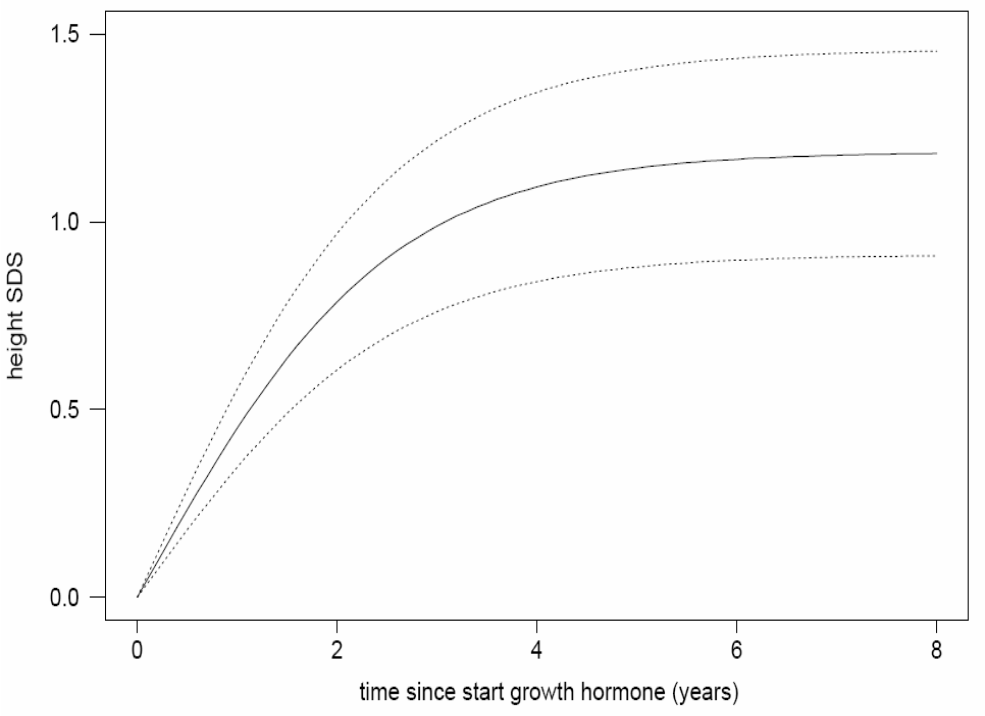

Figure 2. Result of mixed-effect modelling: estimated net effect of GH therapy on development of height SDS in the 20 patients receiving HCT before onset of puberty. Dashed lines represent 95% CI.

Predictive value of parameters of GH secretion

To evaluate the role of GH secreting capacity in impaired growth after SCT, we added different parameters for GH secretion (integrated mean GH concentration, IGF-1 and IGFBP-3) to the mixed-effect model. None of the parameters had a significant effect on either loss of height SDS after SCT or on the increase in height SDS after initiation of GH therapy.

Adverse effects, relapses and secondary tumours

Within 2 weeks after start of therapy, patient nr. 14 repeatedly had urticaria and angioedema after injecting GH and decided to stop GH therapy. Due to increasing aversion of injections, patient nr. 22 decided to stop GH therapy after eight months.

In the 43 untreated patients compensated hypothyroidism was diagnosed in 12 (28%) and autoimmune hypothyroidism in 1 (2%). In the 23 GH treated patients, compensated hypothyroidism was diagnosed in 8 (35%) before start of therapy, and in an additional 8 (35%) after start of therapy. Thyroxine suppletion was initiated in all patients with compensated hypothyroidism.
Five boys and one girl developed exostoses during GH therapy, another boy experienced growth of pre-existing exostoses during GH therapy. In the 43 untreated children, two boy developed exostoses. There was 1 relapse among the 23 GH treated patients (nr 29; treated outside the protocol relapsed 9 month after start of GH therapy), compared to 6 relapses in the 43 untreated children. In the untreated group, one patient developed a schwannoma 7.3 years after TBI. In the GH treated group 2 patients developed a secondary malignancy. Patient 28 developed an osteosarcoma 5.3 years after start of GH therapy (12.7 years after SCT). Patient nr. 22 (treated with GH for only 8 months) developed papillary thyroid carcinoma 3.5 years after start of GH therapy (9.7 years after SCT).

Discussion

This study reports a positive effect of GH therapy on height SDS in children with impaired growth after TBI-based conditioning for SCT, even in the absence of GHD. The calculated net effect (1.1 SD after 5 years of GH therapy) did not correlate to GH secretion status. A potential limitation of our study is the use of single fraction TBI, as most SCT centres use fractionated TBI. As final height results from our centre are comparable to those reported by centres using fractionated TBI, we believe this to be a minor limitation.
GHD was diagnosed in 8 of the 66 patients (12%) monitored since 1997. There is a wide variation in the reported incidence of GHD after TBI-based conditioning for SCT, with incidences from 0 to 84% [3-5;14-27]. Factors contributing to these differences in incidence of GHD are: population size, duration of follow-up, TBI characteristics (dose, dose rate, fractionation), indications for GH testing and selection bias (e.g. exclusion of children with a history of CI or exclusion of children not tested for GHD). In addition, the criteria used for the diagnosis of GHD largely influence the incidence of GHD. If we had used ‘standard’ criteria for GHD (e.g. mean nocturnal GH concentration < 2.5 µg/l or peak GH < 10 µg/l on two occasions, 23 of our 29 patients tested

(79%) would have been diagnosed as having GHD. The vast majority of the studies on GHD after TBI do not mention the GH assay used, nor do they mention the use of assay specific references. We believe that the relatively low incidence of GHD in the present study can be attributed to the absence of children with additional CI as well as to the use of assay-specific criteria for the diagnosis of GHD.

Most patients included in the present study showed a decrease in height SDS between TBI and start of GH therapy (figure 1). A continuing decrease in height SDS could be expected based on previous reports in the literature as well as our model for growth after TBI. However, in most of the patients treated with GH, height SDS at last visit (mean follow-up of 4.4 years) was comparable to height SDS at start of therapy (table 3).

Data on the effect of GH therapy on height after TBI-based conditioning for SCT are limited, with only 3 studies reporting final height [2;4;5]. The first study by Cohen et al. is a questionnaire-based study on final height after pre-pubertal SCT in the European EBMT centres, showing no significant difference in final height between GH treated an non-GH treated patients [2]. Due to the set-up of the study, no information was available on the indications for GH therapy, the GH doses used or the changes in height SDS after start of GH therapy. Therefore, no valid conclusions can be drawn from this study regarding effect of GH therapy. The second study by Frisk et al. reports final heights of 11 patients treated with GH after TBI and autologous SCT for ALL (6 had received additional CI and one CSI). In that study, 6/11 GH treated patients were considered to have GHD based on maximum GH peak in 12- or 24-hour spontaneous GH secretion profiles. The GH assay (and probably also the reference standard) was the same as in the present study, but the cut-off for the diagnosis of GHD was much higher (maximum GH < 10 µg/l vs 5.3 µg/l in our study). According to multiple regression analyses, the effect of GH therapy on height SDS was 0.18 SDS for each year of GH therapy. The third study by Sanders et al. reports the effect of GH therapy on 'final height' (height at the age of 16 years) of 90 TBI patients (32 CI) diagnosed with GHD, 42 of whom (21 CI) were treated with GH (20 - 30 µg/kg/day). According to multiple regression analysis, GH treatment resulted in 0.86 SD increase in final height in the 35 children with SCT before the age of 10 years, whereas no significant effect of GH therapy was found in the 7 children receiving SCT after the age of 10 years.

The estimated net effect of GH therapy on height SDS in our study (1.1 SDS after 5 years) is comparable to that reported by Sanders et al. in children receiving SCT before the age of 10 years (0.9 SD), as well as to that reported by Frisk et al. (0.18 SD/year). Major differences with these previous studies are that the majority of the patients in the present study were not considered GH deficient (although diagnostic criteria differ between the studies [28]), and that the estimation of the effect in the present study is based on mixed-effect modelling, a robust statistical method that allowed us to predict individual height SDS curves and compare those to actual height SDS after start of GH therapy without the risk of significant bias and without the need for final height in all patients.

We also looked at the influence of GH secretion status on either decrease in height SDS until testing and on the effect of GH treatment. The results of GH secretion status did not correlate with decrease in height SDS before GH therapy or with response to GH therapy. This suggests that impaired growth after SCT is mainly caused by radiation damage to the epiphyseal growth plate (and thus end-organ sensitivity) and far less by decreased GH secretion.

The incidence of (sub-clinical) hypothyroidism was more than twice as high in the GH treated patients compared to the non-treated patients. The reported incidence of radiation induced hypothyroidism after TBI in children is 15-50% and seems to be higher after unfractionated TBI [29]. In GH deficient children, GH replacement therapy does not induce primary hypothyroidism. It either reveals previously unrecognised cases of central hypothyroidism or induces hypothyroxinaemia by increased conversion of thyroxine to tri-iodothyronine [30-32]. None of our patients had central hypothyroidism, however, and the majority of cases were not GH deficient. The higher incidence of compensated hypothyroidism in GH treated survivors of TBI is in line with the results of Sanders et al. [5]. A possible explanation for this higher incidence of hypothyroidism in GH treated children could be that in GH treated patients thyroid function was monitored more closely, or that increased growth increased the demand for thyroxine.

The risk of secondary cancers is increased in all survivors of TBI-based conditioning for SCT during childhood and cumulative incidence increases with time after SCT and in case of younger age at SCT [33]. Although surveillance studies do not suggest an increased risk of disease recurrence in survivors of childhood cancer by GH therapy, potential oncogenic effects of GH remain a

concern [34;35]. In supra-physiological doses both GH and IGF-I stimulate proliferation and differentiation of both normal and leukaemic cultured human lymphocytes [36;37], more physiological concentrations of GH (i.e. less than 50 ng/mL), however, do not have an effect on colony formation, nor on the number of colonies or DNA-synthesis in cultured leukaemic cells. In the present study, two of the 23 GH treated patients developed a secondary tumour (one thyroid carcinoma and one osteosarcoma), compared to 1 out of the 43 untreated patients.

Relapse of leukaemia occurred less frequently in the GH treated patients (1/23) compared to untreated patients (6/43; including one patient who considered starting GH therapy when his leukaemia relapsed almost 5 years after SCT).

Nine of our 66 patients (13.6%, only one female) developed exostoses (believed to be osteochondromas). Exostoses were more frequent in the GH treated group (7/23, 30%) compared to the non-treated group (2/43, 4.7%). Osteochondromas develop in 9-23% of children with TBI-based conditioning for SCT [38-40]. A role for GH therapy in promoting their development is suggested, but malignant degeneration is believed to be rare [5;38-40].

In conclusion, our study shows that recombinant human GH (± 33 µg/kg/day) has a positive effect on height SDS after SCT, even in the absence of GHD. We could not establish a relation between decrease in GH secretion and either impaired growth after SCT or response to GH therapy (probably due to interference of growth plate damage). We therefore believe that evaluation of GH secretion has limited value in predicting the response to GH therapy, and treatment could be considered in every patient with severe growth impairment after TBI, even in the absence of GHD. Patients should be informed about the increased risk of secondary tumours after SCT and the concerns of oncogenic potential of GH therapy, as well as about the possibility of increased risk of osteochondromas.

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