

CLINICAL STUDY

Adult final height after GH therapy for irradiation-induced GH deficiency in childhood survivors of brain tumors: the Belgian experience

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Abstract

Objectives: The treatment of brain tumors in childhood is frequently complicated by growth retardation with a high proportion of irradiation (Irr)-induced GH deficiency (GHD) resulting in reduced adult final height (AFH) even after GH therapy (GHT). In order to optimize future GHT protocols, more information on the factors influencing the growth response to GH in these children is needed.

This retrospective study evaluated AFH and influencing auxological and treatment factors of a standardized daily biosynthetic GHT in childhood survivors of brain tumors with documented GHD after brain Irr.

Design and methods: From the Belgian GH Registry, 57 children survivors of a brain tumor outside the hypothalamo-pituitary area with available AFH were stratified into two groups depending on cranial (C-Irr; $n=25$) or craniospinal (CS-Irr; $n=32$) Irr.

Results: In the C-Irr patients, results showed an AFH of -0.8 ($-2.5, 1.4$) SDS (median (range)) and in the CS-Irr patients, results showed a significantly ($P<0.001$) lower AFH of -1.8 ($-4.2, 0.0$) SDS. AFH SDS corrected for mid-parental height (MPH) in the C-Irr group was -0.5 ($-2.2, 0.9$) and -1.5 ($-3.6, 0.0$) SDS in the CS-Irr group. AFH was positively correlated with age at end of tumor therapy, height SDS at start GHT, height gain SDS first year GHT, and negatively correlated with CS-Irr.

Conclusions: GHT failed to restore adult height to MPH in nearly half of Irr-induced GHD patients for brain tumor, especially those receiving CS-Irr, irradiated at a younger age or shorter at start GHT.

European Journal of Endocrinology 162 483–490

Introduction

The treatment of brain tumors in childhood is frequently complicated by growth retardation with a high proportion of irradiation (Irr)-induced GH deficiency (GHD) resulting in reduced adult final height (AFH).

Although GH has been substituted in those patients for several decades, their AFH remains reduced compared to their genetic potential. In order to optimize future GH treatment (GHT) protocols, more information on the factors influencing the growth response to GH in these children is needed. Until now, it has remained a challenge to determine the effectiveness of different growth-promoting strategies and more studies following the patients up to AFH are needed.

Indeed, only few detailed studies have provided data on FH using different methods or analyzing different populations (1–8). Most of them included a limited number of patients, treated with extractive human GH, with a low frequency and dosage regimen, or with no standardized GH dose. Some of these studies reported FH data without comparison to adult references or without correction for parental height, or included patients treated with GnRH agonist and patients with precocious puberty (PP).

In this retrospective study we analyzed the AFH of Belgian children survivors of a brain tumor after Irr-induced GHD, treated with standardized doses of daily s.c. injections of biosynthetic GH. We examined not only the AFH and the AFH corrected for

mid-parental height (MPH) but also the auxological parameters influencing these outcomes. Given the well-known deleterious effect of spinal Irr on the growth response to GH, we divided the patients into two groups: patients who received cranial Irr (C-Irr) and those who received craniospinal-Irr (CS-Irr).

Subjects and methods

The patients were retrieved from the Belgian GH Registry. This registry contains the data of about 2000 children and adolescents treated with GH and was followed by the members of the Belgian Study Group for Pediatric Endocrinology (BSGPE). A first selection of 80 patients was made on the following criteria: brain irradiated patients for a tumor outside the hypothalamo-pituitary area, treatment with daily injections of biosynthetic GH, and GHT stopped. Additional inclusion criteria for the present analysis were:

- i) FH available as defined by a height velocity (HV) the last year < 2 cm/year. In total, 11 patients did not fulfill this criterion: eight patients experienced a recurrence, of which six died and two were not followed until FH. The three other patients were lost to follow-up.
- ii) GHD documented by at least one GH stimulation test. This was not the case for one patient who had a plasma GH peak > 10 ng/ml.
- iii) Minimal duration of GHT of 1 year and at least 6 monthly auxological follow-up. Two patients were respectively treated only for 7 and 9 months.

The exclusion criteria were genetic syndromes with short stature: nine patients with a Von Recklinghausen disease were not included in this analysis.

After this second selection, 57 patients from eight centers remained eligible for the present analysis. GH treatment was started between 1988 and 2003 and stopped between 1999 and 2006.

As shown in Table 1, the patients were divided into two groups: one group received C-Irr ($n = 25$, 16 males) and the other group was treated with CS-Irr ($n = 32$; 24 males). All patients of both groups (except one in the CS-Irr group) underwent a surgical removal of their tumor. The tumor diagnoses are reported in Table 1. In the C-Irr group, the patients received a median radiation dose on the brain of 50 Gy (range 20–60 Gy). The dose received by the pituitary could not always be retrieved from the file, dating from 1979 to 1986. In the CS-Irr group, the median radiation dose was 54 Gy (range 44–56 Gy) on the brain and 34.5 Gy (range 24–36 Gy) on the spine. Half of the patients in C-Irr group ($n = 12$), and 60% in the CS-Irr group ($n = 19$) received chemotherapy. Chemotherapeutic agents could not be retrieved from all the files of the patients treated before the year 2000. The most received agents were vincristine, carboplatinum, cyclophosphamide, ifosfamide, etoposide, adriamycin, procarbazine and VP-16.

GHD was diagnosed by standard auxological and biological criteria, which consisted of HV below the 25th centile (calculated from measurements in the previous 6 up to 18 months) and a peak plasma GH level below 10 ng/ml after at least one provocative test (glucagon and/or insulin stimulation tests). As reported in Table 1, multiple hormone deficiencies were present in four patients of the C-Irr group and in 11 patients of the CS-Irr group. In the C-Irr group, three patients were treated with thyroxine, three with hydrocortisone, and one with testosterone injections. In the CS-Irr group, nine patients were treated with thyroxine and two with hydrocortisone. Biosynthetic human GH (Genotonorm, Norditropin, and Humatrope) was given subcutaneously, once daily, at bedtime, in a mean (\pm s.d.) dose of 26 ± 6 μ g/kg. These patients were followed in a similar way in all eight centers: standing height was measured with a Harpenden stadiometer in each center, and the GH dose was adjusted every 3 months to body weight. Anthropometry and pubertal scoring was carried out from the start of GHT every 3 months. Pubertal status was assessed according to Tanner (9).

Table 1 Baseline characteristics of the patients of the cranial irradiation (C-Irr) and craniospinal irradiation (CS-Irr) groups.

	C-Irr group ($n = 25$)	CS-Irr group ($n = 32$)	
Male/female	16/9	24/8	NS
Type of tumor	Astrocytoma ($n = 9$) Ependymoma ($n = 2$) Glioma ($n = 2$) Rhabdomyosarcoma ($n = 7$) Gangliocytoma ($n = 1$) Glioblastoma ($n = 1$) Retinoblastoma ($n = 1$) Osteosarcoma ($n = 1$) Mesencephalic tumor ($n = 1$)	Medulloblastoma ($n = 30$) Astrocytoma ($n = 1$) Ependymoma ($n = 1$)	
Chemotherapy (yes/no)	12/13	19/13	NS
Isolated GHD/multiple hormone deficiencies	21/4	21/11	NS
Mid-parental height SDS	0.0 (–1.5, 1.7)	–0.1 (–1.9, 1.6)	NS

Data on upper/lower segment ratios were not available in the registry because they were not assessed systematically and uniformly in each center.

Height SDS was calculated using the reference standards of Freeman & Cole (10, 11). Height loss SDS between end tumor therapy and start GH treatment was calculated as height SDS at start of GHT minus height SDS at end of tumor therapy. FH was considered to have been reached when HV during the preceding year was <2 cm and transformed in SDS for the actual chronological age of the patient. AFH SDS was defined by the FH in cm reported for a chronological age of 22 years and calculated in SDS. MPH was calculated as (father's height SDS + mother's height SDS)/2. The target height range used was $MPH \pm 1.3$ SDS (12). AFH corrected for MPH was calculated as the AFH SDS minus the MPH. Total height gain in SDS was calculated as the AFH SDS minus height SDS at onset of GHT.

The onset of puberty was defined as the recording of breast stage 2 in girls and a testicular volume of 4 ml in boys (9). PP was defined as the onset of puberty before the age of 8 years for girls and 9 years for boys. Pubertal height gain SDS was defined as AFH SDS minus height SDS at the start of puberty.

Statistical analysis

Results are expressed as median (range) or mean \pm s.d. Continuous variables were compared between the groups by Student's *t*-test or Mann–Whitney–Wilcoxon test, while χ^2 test was used for categorical variables. Correlation between AFH and various auxological parameters was assessed by Pearson coefficient. A multiple linear regression model with stepwise selection of variables was fitted to describe at most the variability of AFH. In the performed regression analysis, we have only considered the main effects of the parameters as predictive factors, because it seemed that the great number of possible interactions with respect to the relatively small number of patients would not allow us to estimate sufficiently stable regression coefficients.

All statistical tests are two-tailed. A *P* value of <0.05 was considered statistically significant. The analysis was performed by SPSS 15.0 software (SPSS Inc., Chicago, IL, USA).

Results

The changes in height SDS from end of tumor therapy until FH are represented in Fig. 1.

At start of tumor therapy

As shown in Table 2, the chronological age at start of tumor therapy was similar in both groups but the height SDS was lower ($P=0.039$) in the CS-Irr group (-0.3 ($-2.6, 1.6$)) than in the C-Irr group (0.4 ($-1.8, 1.8$)).

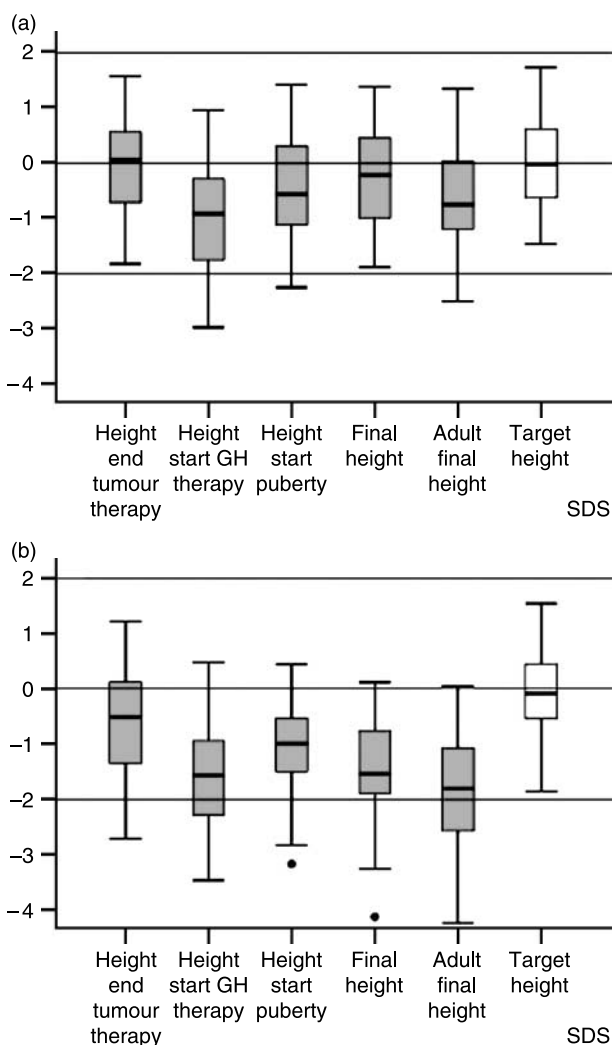


Figure 1 Evolution of height SDS before and during GHT in the C-Irr group (a) and in the CS-Irr group (b). The boxes show the median, the 25 and 75th percentiles. The interquartile range (IQR) is the difference between the 75th (3rd quartile) and the 25th percentiles (1st quartile). The whiskers connect the minimum and the maximum values. Values which fall 1.5 IQR lower than the 1st quartile or 1.5 IQR higher than the 3rd quartile are considered as outliers.

At end of tumor therapy

Table 2 shows that the chronological age at the end of tumor therapy was similar in both groups but the height SDS at end of tumor therapy was lower ($P=0.05$) in the CS-Irr group (-0.5 ($-2.7, 1.2$)) than in the C-Irr group (0.0 ($-1.8, 1.6$)). The patients were all prepubertal except two patients in each group.

At onset of GHT

Table 2 shows also that chronological age at onset of GHT for the two groups was similar. Half of the patients in each group were already in puberty. Height SDS at

Table 2 Clinical and auxological data of cranial irradiation (C-Irr) and craniospinal irradiation (CS-Irr) patients (median (range)).

	C-Irr group (n=25)	CS-Irr group (n=32)	
At start of tumor treatment (n=48)			
Age (years)	6.3 (0.6, 11.0)	5.8 (1.1, 14.9)	NS
Height SDS	0.4 (−1.8, 1.8)	−0.3 (−2.6, 1.6)	P=0.039
At end of tumor treatment (n=54)			
Age (years)	6.8 (0.7, 12.4)	6.1 (1.4, 15.4)	NS
Height SDS	0.0 (−1.8, 1.6)	−0.5 (−2.7, 1.2)	P=0.050
Time interval between end tumor therapy—start GHT (years; lag time)	3.6 (1.3, 9.4)	4.0 (1.5, 11.5)	NS
Height loss SDS between end tumor therapy—start GHT	−0.8 (−2.5, 0.3)	−0.7 (−2.6, 0.2)	NS
At start of GHT			
Prepubertal/pubertal (n)	12/13	17/15	NS
Age (years)	10.9 (4.4, 14.9)	11.2 (4.5, 17.0)	NS
Height SDS	−0.9 (−3.0, 1.0)	−1.6 (−3.5, 0.5)	P=0.025
At start of puberty			
Age (years) boys	11.8 (9.2, 14.4)	11.9 (9.9, 14.9)	NS
Age (years) girls	9.8 (8.2, 12.5)	9.9 (7.1, 14.8)	NS
Height SDS	−0.6 (−2.2, 1.4)	−1.0 (−3.2, 0.5)	P=0.010
At final height			
Age (years)	17.1 (14.0, 21.0)	17.6 (14.3, 21.4)	NS
FH SDS	−0.2 (−1.9, 1.4)	−1.5 (−4.1, 0.1)	P<0.001
AFH SDS	−0.8 (−2.5, 1.4)	−1.8 (−4.2, 0.0)	P<0.001
AFH corrected for MPH SDS	−0.5 (−2.2, 0.9)	−1.5 (−3.6, 0.0)	P<0.001

start of GHT was significantly ($P=0.025$) higher in the C-Irr group -0.9 ($-3.0, 1.0$) than in the CS-Irr group -1.6 ($-3.5, 0.5$). Time interval between tumor therapy and start of GHT (lag time) and height loss SDS during this period were not statistically different between the two groups. We did not observe a reduction in the lag time during the study period (1988–2006).

During GHT and pubertal development

Mean GH dose (26 ± 6 $\mu\text{g/kg}$ per day) and median duration of GHT 4.7 (1.4, 10.6) years were not different between the two groups. A significant increase in HV during the first year of GHT was observed in both groups, although the growth response was significantly ($P=0.026$) greater in the C-Irr (9.9 (2.8, 12.5) cm/year) compared to the CS-Irr group (7.8 (3.5, 11.1) cm/year). On the other hand, the change in height SDS during the first year of GHT was similar in the two groups (0.7 ($-0.3, 1.2$) versus 0.5 ($-0.3, 1.0$)).

Table 2 shows that the chronological age at the start of puberty was similar in the two groups: respectively in the C-Irr and in the CS-Irr groups: 9.8 (8.2, 12.5) and 9.9 (7.1, 14.8) years for girls and 11.8 (9.2, 14.4) and 11.9 (9.9, 14.9) years for boys. In the CS-Irr group, two patients were treated with a GnRH agonist (Decapeptyl) for PP, while in the C-Irr group, one patient with an early puberty was treated with Decapeptyl.

Considering only those patients who remained prepubertal during at least 1 year of GHT ($n=8$ in the C-Irr group, $n=11$ in the CS-Irr group), prepubertal height gain SDS was respectively $+1.4$ (0.2, 1.9) and $+0.8$ (0.2, 1.7) during a median time of 2.7 (1.5, 6.7)

and 1.9 (1.0, 3.6) years in the C-Irr and CS-Irr groups. When analyzing the growth of these patients from start of puberty until AFH, a comparable height loss SDS in the C-Irr and in the CS-Irr group was observed: respectively -0.8 ($-1.5, 0.0$) and -1.0 ($-1.6, 0.6$) during a median time of 4.0 (1.8, 5.9) and 4.6 (1.7, 7.9) years.

At final height

GH treatment in the CS-Irr patients resulted in a significantly ($P<0.001$) lower AFH (-1.8 ($-4.2, 0.0$) SDS) than in the C-Irr patients (-0.8 ($-2.5, 1.4$)). Boys reached a median AFH of 172.2 (161.0, 186.2) cm and 165.5 (149.0, 175.5) cm respectively in the C-Irr and CS-Irr groups; girls reached an AFH of 163.2 (153.0, 172.0) cm and 154.4 (147.5, 164.1) cm respectively. Also the AFH corrected for MPH was significantly ($P<0.001$) lower in the CS-Irr group: AFH corrected for MPH was -0.5 ($-2.2, 0.9$) SDS in the group of 25 C-Irr children and -1.5 ($-3.6, 0.0$) SDS in the 32 CS-Irr patients. We did not observe an improvement in AFH over the study period (1988–2006).

The AFH was not different between the patients who were already in puberty at the start of GHT and those who were not. Two of the 25 C-Irr patients (8%) and 12 of the 32 (38%) of the CS-Irr patients did not reach an AFH within the normal population range (between -2 SDS and $+2$ SDS). Six of the 25 C-Irr patients (24%) did not reach an AFH > -1.3 s.d. for the MPH, while this was the case for 19 (59%) of the 32 CS-Irr patients.

Table 3 Pearson correlation between adult final height (AFH) SDS and auxological variables.

Variable	R value	P
Age at start of tumor therapy	0.20	NS
Age at end of tumor therapy	0.23	NS
Height SDS at start of TT	0.52	$P<0.001$
Height SDS at end of TT	0.56	$P<0.001$
Time between end TT and start GHT (lag time)	−0.36	$P=0.006$
Height loss SDS between end TT and start GHT	0.22	NS
Height SDS at start GHT	0.71	$P<0.001$
Age at start GHT	0.01	NS
Year start GHT	0.01	NS
Height velocity (cm) first year GHT	0.39	$P=0.003$
Height gain SDS first year GHT	0.32	$P=0.002$
Prepubertal height gain SDS	0.01	NS
Age at start of puberty	−0.02	NS
Height SDS at start of puberty	0.67	$P<0.001$
Pubertal height gain SDS	0.54	$P<0.001$
MPH SDS	0.45	$P=0.001$
Dose of GH	−0.21	NS

TT, tumor therapy.

Total height gain in SDS was limited in both groups but was significantly higher ($P=0.002$) in the C-Irr group (0.5 (−0.9, 1.5)) than in the CS-Irr group (−0.4 (−1.5, 1.5)) who even experienced a loss in height SDS.

As shown in Table 3, AFH (SDS) in the GH-treated irradiated children was not only positively correlated to the height at onset of GHT, the height SDS at onset of puberty, the height SDS at the start and at the end of the tumor therapy but also to the pubertal height gain SDS, the growth response during the first year of GHT (in cm or SDS) and the MPH. On the other hand, a negative correlation was found with the time lapse between the end of oncologic therapy and the onset of GHT (lag time). Growth response was not affected by all other parameters documented in Table 3 or by chemotherapy and gender.

The variables considered for multivariate analysis were: type of Irr (cranial or craniospinal), gender, chemotherapy, type of (single or multiple) hormonal deficiency, and all major auxological parameters as described in Table 3. The multiple regression model that describes at most the variability of AFH (SDS) is as follows: $\text{AFH (SDS)} = -0.98 - 0.75 \text{ (CS-Irr)} + 0.08 \text{ (chronological age at end of tumor therapy)} + 0.69 \text{ (height SDS start GHT)} + 0.97 \text{ (height gain SDS first year GHT)}$; $R^2=0.72$; $P\leq 0.002$ for all variables). Including gender, chemotherapy, lag time, and age at start of puberty in the multiple regression analysis did not make a significant contribution ($P=0.14$, $P=0.18$, $P=0.94$ and $P=0.14$ respectively) to the prediction model of AFH (SDS).

Discussion

Decreased FH is a common outcome after successful treatment of children with brain tumors, even after GHT.

Reporting detailed AFH growth data in brain irradiated children is essential to document the outcome of changing treatment protocols, but also to outline the benefits of new growth promoting strategies and setting up prospective studies. Previous studies have attempted to correlate patient characteristics and treatment parameters with FH outcome. Our study reports the FH of the largest number of GH-treated children after C-Irr or CS-Irr for a brain tumor using a standardized GH replacement protocol with exclusively daily biosynthetic GHT. The literature reports mainly data of children with a combination of different GH treatment protocols (3–7 injections/week, different doses, extractive or biosynthetic GH).

In addition to reporting FH data, we aimed to report also the AFH to avoid overestimating the FH data expressed in SDS and thereby overestimating the benefits of GHT. For example, the FH SDS of a boy with 165 cm stopping growing at 16 years is −1.1 SDS but his AFH will be −1.9 SDS at 22 years of age. The present study documented an AFH corrected for MPH of −0.5 (−2.2, 0.9) SDS in the 25 C-Irr children and −1.5 (−3.6, 0.0) SDS in the 32 CS-Irr patients. These results confirm that in children with GHD after cranial and especially CS-Irr, GHT is unable to restore height completely to their target genetic height. Indeed, whereas 76% of the C-Irr reached an AFH above −1.3 s.d. for the MPH, only 41% of the CS-Irr obtained their genetic height potential. In the literature, we did not find FH data corrected for adult height data for eventual comparison with our findings.

As noted in Table 4, our FH results are much better than previous center-based studies published before 2000 (1–4). Compared with more recent center studies (6, 7), our patients reached nearly the same FH without using higher doses of GH than substitution of GHD or instituting a widespread use of GnRH analog in combination with GHT in case of early puberty. GH treatment modality such as dose, frequency, and type of GH might explain at least in part our better result as suggested in the literature by Gleeson *et al.* (7). Indeed, all our children have been treated with daily and biosynthetic GH injections. However, since all the children in our study received the same dose of GH (0.18 mg/kg per week), we cannot comment on a dose-related effect of GHT in our study. Xu *et al.* (6) supports the use of higher doses (0.3 mg/kg per week) of GH as their FH data were better than previously reported in Europe (3, 4, 13) with lower doses (0.15 mg/kg per week). They even speculated that a higher dose (0.7 mg/kg per week) in puberty should be of interest to promote better adult height in children treated with CS-Irr and chemotherapy trying to counteract the well-known loss of spinal growth during puberty (14–16). However, our study showed that using half of the doses of Xu *et al.*, similar FH data were obtained. Up to now, improving spinal growth by giving higher GH dose in CS-Irr patients during puberty remains

Table 4 Final height (FH) SDS among Belgium childhood survivors of brain tumors treated with GH for irradiation (Irr)-GHD and previously reported studies in the literature.

(a) Cranio-spinal irradiation	n	Height SDS (mean)	Tumors	MPH SDS	GH dose
BSGPE (2010)	32 (24 M)	Start GH -1.6^a (11.2 years) FH -1.5^a AFH -1.8^a	Medullo (30)/varia (2)	-0.1^a	0.18 mg/kg per week daily 2 GnRH α
Clayton (1988) (1)	8 (5 M)	Start GH -2.4 (11.4 years) FH -3.4	Brain tumors distant from pit-hyp axis	-0.2	4 IU 3 inj/week = 1.3 mg 3 inj/week
Sulmont (1990) (3)	18	Start GH -2.5 (11.2 years) FH -3.7	Medullo	NA	0.3–0.4 IU/kg per week 3 inj/week = 0.1–0.13 mg/kg per week 3 inj/week
Ogilvy-Stuart (1995) (4)	9 CS-Irr 6 CS-Irr + chemo	FH NA Height loss between FH and MPH 17 cm 24.5 cm	Brain tumors distant from pit-hyp axis	NA	<'85: 5 mg pGH 3 inj/week >'85: 4 IU 3 inj/week >'88: 0.5 IU/kg per week = 0.17 mg/kg per week daily
Adan (2000) (5)	9	Start GH -1.7 (9.2 years) FH -2.0	Medullo	0.4	0.4–0.6 IU/kg per week daily = 0.13–0.2 mg/kg per week daily 4 GnRH α
Xu (2003) (6)	27 (21 M)	Start GH NA (11.3 years) FH -1.9	Medullo	0.0	0.3 mg/kg per week daily 6 GnRH α
Gleeson (2003) (7)	25 CS-Irr 16 CS-Irr + chemo	Before '88 FH -3.5 After '88 FH -1.4 Before '88 FH -3.7 After '88 FH -2.8	Brain tumors distant from pit-hyp axis	NA	<'85 5 mg pGH 3 inj/week >'85 4 IU 3 inj/week >'88 0.5 IU/kg per week = 0.17 mg/kg per week daily 6 GnRH α
Ranke (2007) (8)	111 (61 M)	Start GH -2.2^a (8.7 years) FH -2.3^a	Medullo	NA	0.19 mg/kg per week 3–7 inj/week
(b) Cranial irradiation	n	Height SDS (mean)	Tumors	MPH SDS	GH dose
BSGPE (2010)	25 (16 M)	Start GH -0.9^a (10.7 years) FH -0.2^a AFH -0.8^a	Brain tumors distant from pit-hyp axis	0.0 a	0.18 mg/kg per week daily 1 GnRH α
Clayton (1988) (2)	7 (2 M)	Start GH -1.8 (11.6 years) FH -2.2	Brain tumors distant from pit-hyp axis CNS prophylaxis ALL	-0.6	4 IU 3 inj/week = 1.3 mg 3 inj/week
Sulmont (1990) (3)	5	Start GH -2.0 (10.6 years) FH -1.7	Face/neck T	NA	0.3–0.4 IU/kg per week 3 inj/week = 0.1–0.13 mg/kg per week 3 inj/week
Ogilvy-Stuart (1995) (4)	6 C-Irr 3 C-Irr + chemo	FH NA Height loss between FH and MPH 7.2 cm 18.4 cm		NA	<'85: 5 mg pGH 3 inj/week >'85: 4 IU 3 inj/week >'88: 0.5 IU/kg per week = 0.17 mg/kg per week daily

Table 4 Continued

(b) Cranial irradiation	n	Height SDS (mean)	Tumors	MPH SDS	GH dose
Adan (2000) (5)	13	Start GH 0.1 (10.4 years) FH -0.7	Various	0.0	0.4–0.6 IU/kg per week daily =0.13–0.2 mg/kg per week daily 12 GnRHa
Gleeson (2003) (7)	10 C-Irr	Before '88 FH -3.1 After '88 FH -1.3	Brain tumors distant from pit-hyp axis	NA	<'85 5 mg pGH 3 inj/week >'85 4 IU 3 inj/week
	7 C-Irr+chemo	Before '88 FH -1.7 After '88 FH -2.8			>'88 0.5 IU/kg per week =0.17 mg/kg per week daily 5 GnRHa

NA, not available; M, male; pit-hyp, pituitary-hypothalamus; pGH, pituitary GH; GnRHa, patients treated with GnRH agonists.

^aMedian.

uncertain. The question remains whether better results can be expected by lowering the spinal dose in case of CS-Irr. However, this option may come at the expense of increased recurrence rates, and current research is also focusing on novel drugs and treatment modalities, such as hyperbaric oxygen therapy and proton beam therapy (17), aiming to reduce the damage on the spine due to radiation therapy.

While there is no doubt for some authors (7, 18) that the FH data are better in 2008 than 25 years ago, it remains difficult to determine which treatment factor is of most importance. They advocate, as already discussed previously, the use of more standardized GH schedules and better dosing regimens but also shorter time intervals between end of oncological treatment and starting GHT and propose a more generalized use of GnRHa in addition to GHT in patients, not only with PP but also with early puberty. Using the available data in the Belgian GH Registry, we could not demonstrate a significant improvement of AFH from 1988 until 2006, the patients having the same delay in instituting GHT and being treated with a similar GH dose and frequency regimen. Although our AFH data are better than other studies, as summarized in Table 4, the time interval between stopping oncologic therapy and starting GHT is not shorter than in other studies (7). Since only three patients in our study were treated with GnRHa, no conclusions can be drawn with regards to the addition of this class of drugs to standard GHT. However, it remains important in the future to demonstrate by using more standardized and prospective methodologies, the additional effect of GnRHa therapy in this population at risk for short adult height.

Previous studies (4, 7) have shown that chemotherapy had an additive adverse effect on FH. In our study, growth response was unaffected by the use of previous chemotherapy. It is probable that differences in chemotherapy regimens may account for the reported variations in growth response to GH. Growth response

was also unaffected by additional pituitary hormone deficiencies. Regarding gender, there are also some divergences between authors (7, 19, 20). Our data do not show any significant difference regarding the response to GH between females and males.

Major weaknesses of this long-term study are the lack of spinal height measurements, related to the lack of a standardized way of measurement (sitting height versus leg length measurements) in the different centers and the absence of grading of compliance with the GHT, both related to the retrospective and multicentric nature of the study.

In conclusion, daily biosynthetic GHT at 0.18 mg/kg per week for Irr-induced GHD in Belgian childhood survivors of brain tumors failed to induce catch-up growth but prevented further height loss. CS-Irr, young chronological age at end of tumor therapy, and short stature at start of GHT were risk factors for being short at AFH. Comparing the FH data available in the literature, our study shows one of the best results, probably related to the inclusion of patients treated only with biosynthetic GHT in a daily regimen.

Declaration of interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This study was funded by a grant of the Belgian Study Group for Pediatric Endocrinology (BSGPE).

Acknowledgements

We thank all the members of the BSGPE for the participation in the execution of the study and helpful discussions.

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Received 4 November 2009

Accepted 30 November 2009