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

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PUBERTAL DEVELOPMENT AND GROWTH AFTER TOTAL-BODY IRRADIATION AND BONE MARROW TRANSPLANTATION FOR HAEMATOLOGICAL MALIGNANCIES

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Abstract

Pubertal development after total-body irradiation (TBI) was investigated in 40 children (21 boys) treated with allogeneic bone marrow transplantation (BMT) for haematological malignancies at a mean age of 11.3 years. The mean age at the last visit was 19.0 years. Twenty-five patients (15 boys) were prepubertal at the time of BMT. Data on secondary sexual characteristics, the pituitary-gonadal axis and longitudinal growth were retrospectively collected from the medical records. In boys not receiving additional testicular irradiation (n = 19), penile growth and pubic hair development was normal and all had serum testosterone levels within the adult range. The majority of them, however, had incidental elevations of LH, suggesting minor Leydig cell damage. Testicular volume at last measurement was small (mean: 10.5 ml) and serum FSH levels were elevated in all boys, with normalisation in only one, suggesting severe impairment of reproductive gonadal function. Of the ten girls who received BMT before puberty, six had a spontaneous onset of puberty and menarche; the four other girls needed hormonal substitution therapy. Recovery of gonadal function after cessation of substitution was seen in one girl, who became pregnant but had a spontaneous abortion. Decrease in height SDS was seen in the majority of patients and was positively correlated with male gender and lower age at the time of BMT.

Conclusion: Careful monitoring of both gonadal function and growth after bone marrow transplantation and total body irradiation is warranted in order to detect disturbances early and ensure normal pubertal development in children treated for haematological malignancies.

Introduction

Over the last two decades bone marrow transplantation (BMT) has become an important treatment modality for haematological malignancies, and a combination of total-body irradiation (TBI) and high-dose chemotherapy is frequently used in preparative regimens for BMT. The main aims of these preparative regimens are: (a) myeloablation in order to enable grafting of donor marrow and (b) the eradication of malignant cells that might have survived previous treatment. Unfortunately, TBI and high-dose chemotherapy have important negative effects on several organs including those of the endocrine system, which may lead to disturbances in both growth and pubertal development after BMT for childhood malignancies [1-3]. As the number of patients with long-term disease-free survival increases, more patients who received BMT during childhood reach adulthood and the final outcome of growth and pubertal development after BMT can be assessed. We previously reported that final height was decreased in patients who underwent BMT for haematological malignancies [4]. In the present study we investigated the effects of TBI and BMT on pubertal development and gonadal function in patients grafted for haematological malignancies during childhood.

Patients and methods

Between 1970 and 1995 148 patients suffering from haematological malignancies received an allogeneic BMT before the age of 16 years at the Department of Paediatrics, Leiden University Medical Centre. Of those patients, 79 were still alive in July 1997, 40 of whom (21 boys, 19 girls) were older than 16 years of age at the time of their last visit. These 40 patients were included in the present study, 16 of whom (10 boys) were also included in the previous study on final height [4]. Patient characteristics are given in table 1.

At the time of BMT, 25 patients were pre-pubertal. The mean age at the time of BMT was 11.3 years (range 0.9-15.9) and at the time of the last examination 19.0 years (range 16.1-25.4).

TBI was delivered by linear accelerator with energies of either 5.0 or 6.0 MV and at a midline instantaneous dose-rate of approximately 23 cGy/min.

Table 1. Patient characteristics

	Prepubertal at BMT		In Puberty at BMT*	
	Boys (n=15)	Girls (n=10)	Boys (n=6)	Girls (n=9)
Age at BMT in years:				
mean; median	9.9; 10.2	8.7; 9.1	13.8; 13.5	14.9; 14.4
(range)	(4.0 - 14.1)	(0.9 – 14.4)	(12.6 - 15.3)	(14.2 - 15.9)
Age at last visit: in years:				
mean; median	18.5; 18.2	19.1; 19.0	18.9; 18.0	19.8; 18.9
(range)	(16.1 – 21.7)	(16.5 – 23.9)	(16.9 - 23.3)	(16.8 – 25.4)
Indication:				
AML	7	7	4	6
ALL	4	1	2	2
CML	-	2	-	1
MD	2	-	-	-
NHL	2	-	-	-
TBI-dose:				
5.0 Gy	-	1	-	-
7.5 Gy	7	5	-	-
8.0 Gy	4	4	1	4
2 x 6.0 Gy	4	-	5	5
Additional Irradiation:				
Testes	2	-	-	-
Cranium	1	1	1	1

* The three male patients with uncertain pubertal status at the time of BMT are included in this category. ALL acute lymphoblastic leukaemia, AML acute myeloid leukaemia, CML chronic myeloid leukaemia, MD myelodysplasia

One girl, who underwent BMT in the 1st year of life, received a single fraction TBI of 5.0 Gy. All other patients undergoing BMT before the age of 10 years received a single fraction TBI of 7.5 Gy. Patients older than 10 years received TBI either as a single fraction of 8.0 Gy (until 1990) or as two fractions of 6.0 Gy each, on 2 consecutive days (from 1990 onwards).

Conditioning regimens included cyclophosphamide (60 mg/kg per day for 2 consecutive days) in all patients. From 1989 onwards, the patients undergoing BMT for myeloid leukaemia (n = 11) also received cytarabine (2 x 1.0 g/m2 day for 2 consecutive days) and patients with BMT for lymphoblastic leukaemia (n = 4) or non-Hodgkin lymphoma (NHL)(n = 1) received etoposide (350 mg/m2 day

for 2 consecutive days). Two boys (both treated before puberty) received an additional testicular irradiation with 10 Gy in four fractions prior to BMT; four other patients had previously received cranial irradiation with a total dose of 18 Gy in 12 fractions (n = 3) or 24 Gy in 18 fractions (n = 1).

Information about pubertal development was obtained from the medical records and consisted of the following data: Tanner stages of breast or genital development and pubic hair [5], testicular volume measured with orchidometer, age at menarche, height measurements, serum levels of LH and FSH and oestradiol in girls and testosterone in boys, data on substitution therapy with sex steroids and on the use of oral contraceptives. 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 clear signs of pubertal development (e.g. penile growth and pubic hair development) had occurred in boys while testicular volume had not reached 4 ml, onset of puberty was determined on the basis of the combination of progression of Tanner stages and increasing serum levels of testosterone. When puberty was induced, the onset of puberty was defined as the start of treatment with sex steroids. In three boys puberty started approximately at the time of transplantation, but unfortunately Tanner stages and testicular volumes at the time of BMT were not recorded.

In girls puberty was induced using increasing doses of ethinyloestradiol (starting dose: 0.05 µg/kg/day). After a period of at least 1 year medroxyprogesterone was added (5 mg/kg/per day for 12 days every 4 weeks). In boys intra-muscular injections of testosterone were used (starting dose 50 mg every 3 weeks, increasing the dosages over a period of 2 years until the adult dose of 250 mg every 3 weeks was reached).

Height data were analysed for patients treated before the onset of puberty who had not received any additional irradiation (12 boys and 9 girls). Height standard deviation scores (SDS) were calculated using Dutch references [6]. Height velocity was calculated as the height increment within a time interval of 0.5-1.5 years and expressed as cm/year. Target height SDS was calculated using the formula: (maternal height + paternal height ±12 cm)/2 + 3 cm [7]. Standard laboratory methods were used for the measurement of serum levels of oestradiol, testosterone, LH and FSH (detection limits: 40 pmol/l, 0.2 nmol/l, 0.1 U/l and 0.1 U/l, respectively).

Differences in continuous variables between groups of patients were analysed with Wilcoxon rank sum tests. The Wilcoxon signed rank test was used to analyse the changes in height SDS. Associations between continuous variables were tested by Spearman correlation analyses and multiple regression analyses were used to determine the independence of the effects noted in bivariate analyses. The significance level was set at 5% in all analyses.

Results

Onset of puberty after BMT

In all boys who had not received additional testicular irradiation, puberty started spontaneously at a mean age of 13.0 years (range 10.0-15.2 years). One of these boys, treated for relapsing NHL at the age of 14.1 years, had a late onset of puberty (age 15.2 years). Hypergonadotrophic hypogonadism developed in the two boys who had received testicular irradiation and puberty was induced at the age of 14.2 and 15.3 years, respectively.

Of the ten girls treated before puberty, six (including the girl who had received cranial irradiation) had a spontaneous onset of puberty at a mean age of 11.0 years (range 9.7-12.7 years). In the remaining 4 girls puberty was induced after hypergonadotrophic hypogonadism had developed. The mean age at start of the induction therapy was 14.1 years (range 13.5-14.7 years). At the time of induction of puberty, bone age (calculated according to Greulich and Pyle) was delayed in all four girls: mean delay 2.2 years (range 1.1-3.0 years).

Progression of puberty and menarche

Puberty, as measured by progression of Tanner stages, developed normally in the 19 boys who did not receive additional testicular irradiation. At the last examination they had all reached Tanner stages G4 or more and P4 or more. Testicular volume increased above 4 ml in all boys with a spontaneous onset of puberty after BMT (range 6-14 ml), but only 7 of those 13 boys reached a testicular volume of ≥ 10 ml. The last recorded testicular volumes in the three boys with uncertain pubertal status at BMT were 12, 12 and 14 ml at the ages of 18.2, 19.7 and 16.9 years, respectively. The last recorded testicular volumes in the boys transplanted during puberty, were 8, 14 and 18 ml at the ages of

17.1, 16.8 and 16.3 years, respectively. Figure 1 represents development of testicular volumes in time after BMT. The mean testicular volume at the last measurement in all boys who had not received additional testicular irradiation was 10.5 ml (mean age 17.4 years).

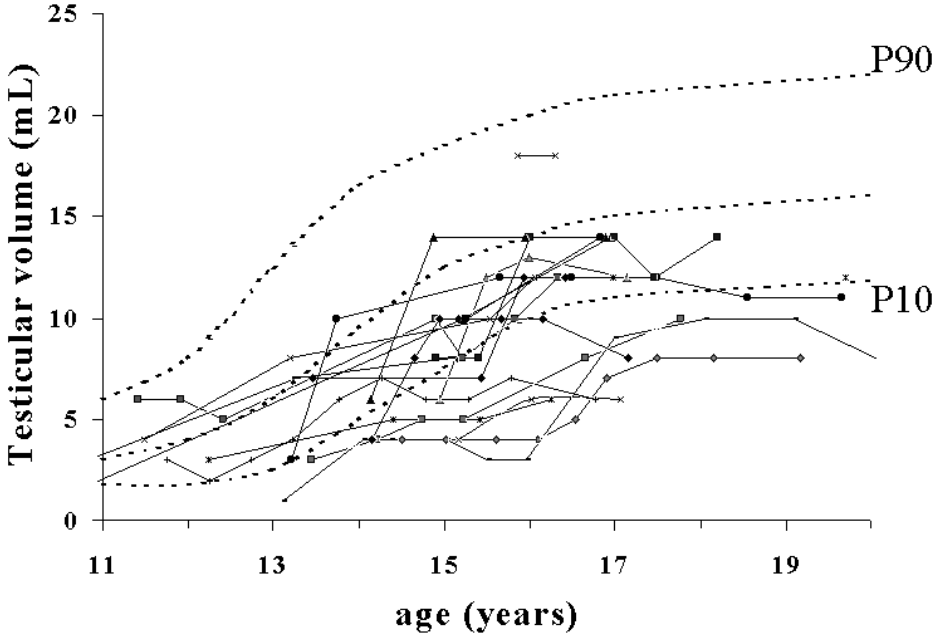

Figure 1. Testicular volume after TBI in boys who did not receive additional testicular irradiation.

The six girls with a spontaneous onset of puberty after BMT had their menarche at a mean age of 12.7 years (range 11.1-14.2 years). Of those six girls, five had a normal progression of puberty and reached Tanner stages B5 and P5 without exogenous oestrogens. The other girl had several transient

episodes of hypergonadotrophic hypogonadism, both before and after menarche. Her pubertal development was delayed and she started using oral contraceptives at the age of 16.5 years, 5 years after menarche (breast development had not progressed beyond Tanner stage B3).
All nine girls treated during puberty developed gonadal insufficiency and required hormonal substitution therapy, making it impossible to assess further spontaneous pubertal development. Before receiving exogenous oestrogens, however, one girl had regression of breast development (substitution started 3 years after BMT), and in another girl breast development had stagnated at the time substitution was started (1 year after BMT). In two of the remaining girls there were insufficient data on breast development and in the other girls substitution therapy was given within several months after BMT.

Endocrine gonadal function and fertility

In the 19 boys who had not received additional testicular irradiation, adult levels of serum testosterone (>15 nmol/l) were reached at any time after BMT (figure 2, upper panel). Episodic elevations of LH (8.1-11.5 U/l), however, were seen in 10 of them (figures 2, middle panel), and in five patients these elevations were accompanied by decreased testosterone levels (9.4-14.8 nmol/l). Elevation of FSH was found in all boys (figure 2, lower panel). In only one patient FSH levels returned to normal (<10 U/l). This patient was pre-pubertal at the time of BMT. Unfortunately, we have no data on spermatogenesis in our patients; to our knowledge none of the male patients has fathered a child.
Disturbances in the pituitary-gonadal axis were seen in all girls, even though six girls had a spontaneous onset of puberty and five of them went through puberty normally. One of these five girls (the only patient that had received a low TBI dose of 5.0 Gy) did not develop hypergonadotrophic hypogonadism, but she did show an abnormal response to a gonadotrophin releasing hormone (GnRH) test. The remaining four girls with a normal progression of puberty developed hypergonadotrophic hypogonadism, defined as elevated levels of serum gonadotrophins without detectable oestradiol. In three of them endocrine gonadal function recovered quickly without oestrogen substitution; the other girl required substitution therapy but she had already reached breast stage B5 at the time gonadal insufficiency was diagnosed (age 14.6 years). All four girls who did not require oestrogen substitution reported having regular

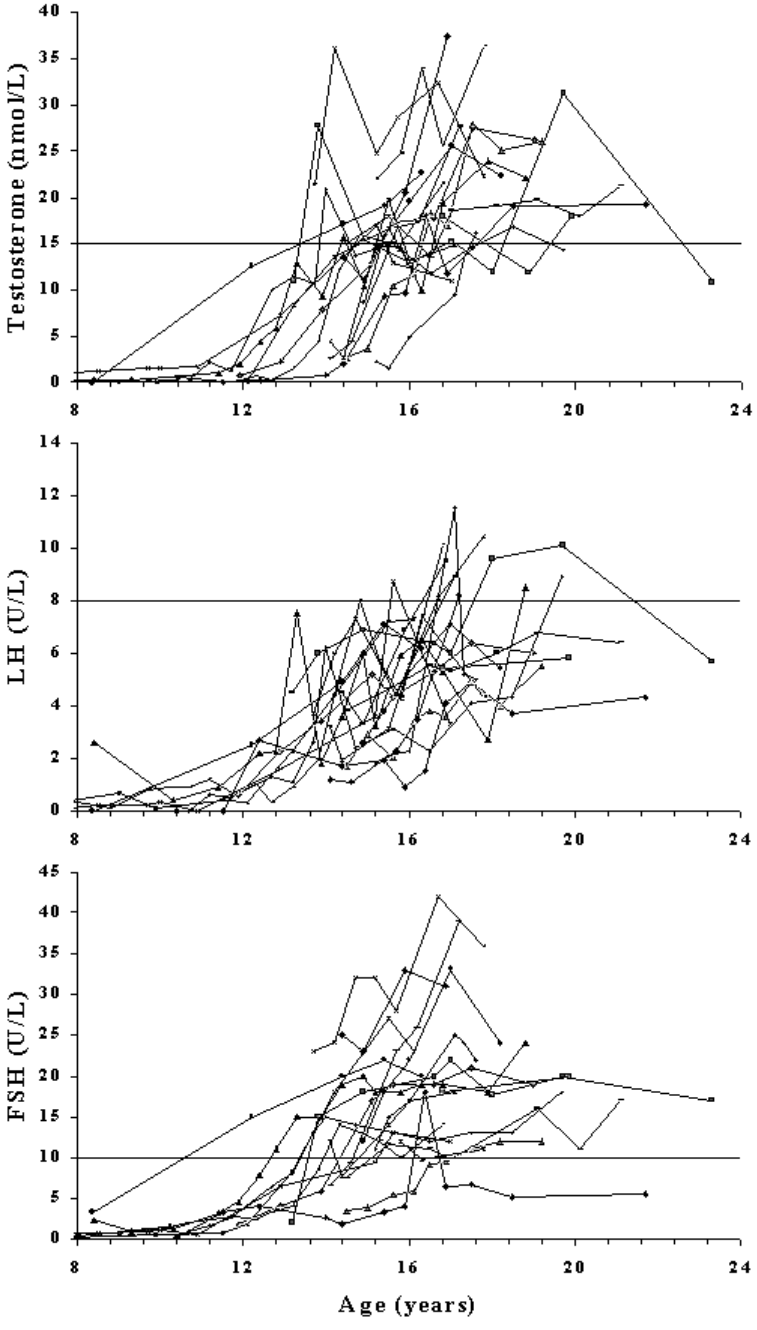

Figure 2. Serum levels of testosterone, LH and FSH after TBI in boys who did not receive additional testicular irradiation.

menses (without the use of exogenous oestrogens) during the last years of their follow up.
The remaining girls (all nine girls undergoing BMT during puberty and the four girls who did not enter puberty spontaneously) developed hypergonadotrophic hypogonadism and received substitution therapy with ethinyloestradiol and progesterone. Recovery of gonadal function after cessation of hormonal substitution was seen in one girl, who received BMT during puberty, but before menarche. This patient later became pregnant twice, both of which resulted in spontaneous abortions.

Growth

At the last examination final height (height velocity <1 cm/year) was reached by 18 of the 21 patients (12 boys and 9 girls) who were treated before puberty and had not received (additional) cranial or testicular irradiation. The other three patients had height velocities of 1.3, 1.5 and 2.1 cm/year. None of the patients were diagnosed with growth impairment due to growth hormone insufficiency or hypothyroidism. Data on (changes in) height SDS at different times after BMT are summarised in table 2.
At the last examination height SDS was significantly lower compared to target height SDS ($P < 0.001$) and compared to height SDS at BMT ($P < 0.001$); the magnitude of these differences in SDS was similar in both sexes. Height SDS also decreased between BMT and the onset of puberty ($P = 0.003$) as well as between onset of puberty and last examination ($P = 0.001$).
When analysed for boys and girls separately, the decrease in height SDS between BMT and onset of puberty was significant in girls only ($P = 0.008$), whereas the mean decrease in height SDS between onset of puberty and last visit was significant in boys only ($P = 0.002$). The total decrease in height SDS was less in the four girls who needed induction of puberty (range 0.1-1.0) than in the five girls with a spontaneous onset of puberty (range 0.9-2.1; $P = 0.05$). These two groups did not differ significantly in age at time of BMT, but the age at onset of puberty was higher in the girls who needed substitution: median 14.0 years (13.5-14.7 years) versus 11.0 years (10.6-12.7 years; $P = 0.014$).

Table 2. Height SDS and changes in height SDS in patients treated before puberty who did not receive additional irradiation

	All patients (n=21)		Boys (n=12)		Girls (n=9)	
	Mean	Median (range)	Mean	Median (range)	Mean	Median (range)
Age at onset of puberty			13.1	13.7 (10.0 to 15.2)	12.5	12.7 (10.5 to14.7)
Height SD Scores						
Target SDS	-0.1	0.3 (-1.8 to 1.1)	-0.2	0.0 (-1.8 to 0.7)	0.2	0.3 (-0.8 to 1.1)
SDS at BMT	-0.2	-0.2 (-1.8 to 1.8)	-0.4	-0.3 (-1.8 to 1.3)	0.1	0.0 (-1.0 to 1.8)
SDS at onset puberty	-0.7	-0.9 (-2.7 to 1.3)	-0.6	-0.7 (-2.0 to 1.0)	-0.7	-1.2 (-2.7 to 1.3)
SDS at last visit	-1.5	-1.7 (-3.6 to 0.9)	-1.9	-2.0 (-3.6 to -0.5)	-1.0	-1.0 (-2.2 to 0.9)
Changes in SD Scores						
from BMT until onset of puberty	-0.5	-0.5 (-1.8 to 0.4)	-0.2	-0.2 (-0.9 to 0.4)	-0.8	-0.9 (-1.8 to -0.1)
from onset puberty until last visit	-0.9	-0.9 (-3.8 to 0.9)	-1.3	-1.0 (-3.8 to -0.1)	-0.2	-0.4 (-1.2 to 0.9)
from BMT until last visit	-1.3	-1.1 (-3.6 to 0.1)	-1.5	-1.6 (-3.6 to -0.3)	-1.1	-1.0 (-2.1 to 0.1)
Difference Target SDS and SDS at last visit	-1.5	-1.6 (-3.0 to 0.3)	-1.7	-1.9 (-3.0 to 0.2)	-1.1	-1.1 (-2.5 to 0.3)

As in our previous analyses, the total loss of height SDS was more severe in patients treated at an earlier age (r = 0.76). A correlation existed, however, between the age at the time of BMT and other factors that could possibly influence final height or loss of height SDS, such as the age at onset of puberty (r = 0.76) or the TBI dose (r = 0.88). A multiple regression analysis of the factors TBI dose, age at BMT, age at onset puberty, gender and need for induction of puberty, revealed that male gender and a younger age at the time of BMT were the only factors with an independent (negative) effect on longitudinal growth.

Discussion

To evaluate the effects of TBI and BMT on pubertal development properly, patients should have completed puberty. As the BMT procedure in patients with haematological malignancies is relatively young, only recently children who have received a BMT before the onset of puberty completed their pubertal

development and reached their final height. As the prognosis for normal pubertal development and gonadal function in survivors of childhood leukaemia treated with chemotherapy alone (i.e. without BMT) is excellent [8;9], disturbances in pubertal development in survivors of BMT and TBI are likely to be the result of irradiation (e.g. total-body, testicular or cranial irradiation) or of (the additive effect of) high-dose chemotherapy used in preparative regimens. Of the hypothalamus-pituitary-gonadal axis the gonads are most vulnerable to damage caused by chemotherapy and/or irradiation; dysfunction of the hypothalamus or the pituitary gland is less common and is almost always associated with cranial irradiation, which can lead to a premature [10-12] as well as a delayed [13] onset of puberty. Our two patients who had received cranial irradiation before the onset of puberty, however, both had a normal timing of puberty.

The spontaneous onset of puberty and the subsequent normal pubertal development in all boys not receiving additional testicular irradiation is in line with the findings of other investigators [1;14;15]. The Leydig cells, responsible for the production of testosterone, are more resistant to irradiation than are spermatogonia, and recovery of Leydig cell function can be seen after absolute radiation doses as high as 24 Gy [14]. The normal pubertal development and the fact that all patients had reached adult serum levels of testosterone at some time after BMT, however, do not necessarily mean that Leydig cells are unaffected. The elevated LH and decreased testosterone levels, incidentally found in the serum of some patients, suggest that TBI can cause subtle changes in Leydig cell function. Other investigators have found decreased responses to HCG stimulation after TBI [3], which further supports this suggestion.

The elevated levels of FSH in all boys and the relatively small testicular volumes indicate that the germinal epithelium of the testis is damaged by the preparative regimens used. In contrast to others [2;16] we did not find a trend towards normalisation of FSH levels in our male patients, even though most patients received single fraction irradiation which is believed to be less detrimental to the testicular germinal epithelium than is fractionated irradiation. This can be explained by the lower total radiation dose used in single-fraction TBI, but there is also evidence that fractionation of one dose may lead to longer sterile periods in man [17]. Variations in the exposure to alkylating agents prior to BMT could be responsible for this absence of testicular recovery, as the

cumulative dosage rather than the daily dosage is the most important factor determining gonadotoxicity of cyclophosphamide, also used in the preparative regimens [16;18;19]. In view of the known vulnerability of germinal epithelium to irradiation and the elevated FSH levels, we expect most of the male patients to be infertile. We have no data on semen analysis in our patients, however, and recovery of spermatogenesis has been described 7 to 8 years after a single fraction of 10 Gy TBI [2]. Moreover, in a group of 463 male TBI patients, Sanders et al. [2] found evidence of testicular recovery in 17% (defined as normal serum levels of LH, FSH and testosterone with evidence of sperm production), and 5 of these patients had fathered one or more children. There was no evidence for increased risk of congenital malformations or complications during pregnancy or delivery. Ovarian damage can be caused by alkylating agents as well as by irradiation. As a total dose of at least 20.0 g of cyclophosphamide is required to produce amenorrhoea in women younger than 30 years of age [2], it is likely that most of the disturbances found in our patients can be attributed to the irradiation and not to the cyclophosphamide used in the conditioning (120 mg/kg).

Gonadal function was less often affected in girls treated before the onset of puberty compared to those treated during puberty. The percentage of girls treated before puberty with a spontaneous onset of puberty and menarche (60%) is comparable with that reported by Sarafoglou et al. (56%) [15], even though their patients had received hyperfractionated TBI. Others have reported slightly lower incidences of spontaneous onset of puberty after TBI between 31% and 45% [15;20]. The finding that all girls treated after the onset of puberty developed gonadal failure is also in line with reports of other investigators [21-23] and suggests that the pre-pubertal ovary is more resistant to irradiation. Attempts to limit radiation-induced damage to the (post-) pubertal ovary using GnRH analogues have been successful in rats [24], but not in rhesus monkeys [25]. As radiation doses used in these animal studies (1 x 30 Gy in rodents and 20 x 2 Gy in monkeys) are higher than those used in TBI, it would be worthwhile to investigate whether the use of GnRH analogues can reduce ovarian damage in patients receiving TBI after the onset of puberty. Recovery of ovarian function occurred in one girl, transplanted for acute myeloid leukaemia (AML) during puberty. She became pregnant twice, but unfortunately both pregnancies resulted in spontaneous abortions. Women receiving high-dose alkylating agents and TBI are at risk for spontaneous

abortions, pre-term delivery and low birth weight infants, as described by Sanders et al. [26]. In this large survey, female TBI patients had a spontaneous abortion rate of almost 40% and the incidence of pre-term labour and delivery was >60%. This is probably caused by radiation-induced changes in the myometrium or uterine vasculature [26;27]. If gonadal function is preserved or recovers, however, patients are still at risk for early menopause [28], as is shown by the girl who had a spontaneous onset of puberty and menarche but later developed secondary amenorrhoea and hypogonadism. As recovery of ovarian function after hypergonadotrophic hypogonadism is possible, hormonal substitution should be stopped at regular intervals in order to re-evaluate gonadal function.

It should be emphasised that patients should be well-informed about the risk of infertility as well as the possibility of (recovery of) fertility and the increased abortion rate in order to allow them to make appropriate decisions about procreation and contraception. In children treated during puberty the possibility of germ cell preservation should be discussed with patients and/or parents.

The use of TBI in preparative regimens for BMT has an adverse effect on growth and final height [4;29;30]. Potential mechanisms include radiation-induced hypothyroidism, growth hormone deficiency and damage to the epiphyseal growth plate [3]. The results of the present height analyses are comparable to the results we reported previously [4]. In this previous study, pre-pubertal linear growth velocity SDS was not statistically different from zero in the first 3 years after BMT. In the present analyses we compared height SDS at the time of BMT to height SDS at the onset of puberty. In all girls and most boys, height SDS at the onset of puberty was lower than at the time of BMT suggesting that loss of height SDS already occurred before the onset of puberty, even when puberty was not delayed. The fact that decrease in height SDS was greater when patients were treated at a younger age, (a result which was found in a European study on final height after BMT as well [31]) further supports the suggestion that height SDS already decreases before the onset of puberty in these patients.

Although there was no significant difference between boys and girls in the decrease in height SDS, in a multiple regression analysis, male gender (but not oestrogen substitution) proved to be an independent factor determining this decrease. Interestingly there was a difference in total loss of height SDS since transplantation between girls who had a spontaneous onset of puberty and

girls who needed induction of puberty. The most likely explanation for this is that, in the case of induction of puberty, the relatively late introduction of relatively low doses of oestrogens had resulted in a prolonged period of growth by delaying progression of bone age, thereby increasing final height. All four girls in whom puberty was induced did indeed have a delay in bone age at the onset of puberty.

We previously suggested that a lack of compensatory increase in peak linear growth velocity, an increase that is present in normal early-developing children, could be responsible for a correlation between age at onset of puberty and decrease in height SDS [4]. Although this is a plausible explanation, we cannot exclude that the correlation between height loss and timing of puberty is caused by selection bias, as only those patients who were not in puberty at the time of BMT were included in the previous (and present) analyses of growth. This way a correlation was created between the age at onset of puberty and the age at BMT, as patients who entered puberty early could only be included if they were treated at a younger age, whereas patients treated at a relatively later age could only be included if they entered puberty late. In the multiple regression analysis the age at onset of puberty did not prove to be an independent factor determining the decrease in height. Therefore, more data are necessary in order to establish the influence, if any, of the timing of puberty on the final height of patients receiving BMT and TBI.

After TBI and BMT for haematological malignancies, pubertal development is normal in most boys, although subtle changes in Leydig cell function can be expected and spermatogenesis is likely to be severely affected. In approximately 50% of girls treated before puberty, pubertal development (and gonadal function) is normal, whereas gonadal insufficiency can be expected in the vast majority of those girls treated after the onset of puberty. As changes in gonadal function are possible and data on long-term prognosis for fertility and endocrine gonadal function are limited, careful follow up remains necessary.

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