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ORIGINAL ARTICLE

Height growth during adolescence and final height after haematopoietic SCT for childhood acute leukaemia: the impact of a conditioning regimen with BU or TBI

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We compared the impact of a conditioning regimen with BU ($n = 16$) or fractionated TBI ($n = 42$) on height growth during adolescence and final height (FH), in 58 adults transplanted for acute leukaemia before adolescence (younger than 9 for girls and 11 for boys, and prepubertal). Heights were measured at three key periods, that is, transplantation, before adolescence, and FH, and compared using height standard deviation score (SDS) and cumulative change in SDS. The influence of the conditioning regimen was assessed using multiple linear regression and adjusting for gender, central nervous system irradiation, age and leukaemia status at transplant and type of transplantation. Overall mean height SDS was near normal at transplantation and before adolescence (0.2 ± 0.1 and -0.2 ± 0.1, respectively), but decreased to -1.6 ± 0.1 at FH. There were significant differences between the TBI and BU groups when comparing FH SDS (-1.8 ± 0.2 vs -0.8 ± 0.2, $P = 0.001$), mean change in height SDS from transplantation to FH (-2 ± 0.1 vs -1.1 ± 0.2, $P = 0.002$) and mean change in height SDS during adolescence (-1.6 ± 0.1 vs -0.7 ± 0.2, $P = 0.003$). We conclude that preparations involving BU, although less toxic than TBI-containing regimens, also have adverse effects on growth, predominantly during adolescence.

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Introduction

Haematopoietic SCT (HSCT) in children may result in impaired growth and reduced adult height. Growth failure in children who have undergone HSCT for acute leukaemia is a multifactorial process implicating first-line treatments for acute leukaemia,[1–4] post transplant complications and their consecutive treatments, especially GVHD requiring prolonged use of steroid, and myeloablative conditioning regimens. Conditioning regimens seem to alter growth throughout the combined effects of lesions of the hypothalamic–pituitary gland axis, multiple endocrine dysfunction (essentially thyroid and gonadal) and damage to the bone epiphyses.[5–10]

In healthy children, growth velocity peaks at adolescence, resulting in a gain of height crucial for determining final adult height. Few studies have reported the impact of TBI on pubertal growth.[11–14] Yet, to our knowledge, the effect of preparation without TBI on growth during this period has never been described. In this study, we compared the impact of a conditioning regimen with BU or TBI on height growth during adolescence and on final height (FH).

Materials and methods

Patients

Patients described here were all included in a long-term follow-up programme for childhood acute leukaemia survivors. This programme, known as 'L.E.A.' (for 'Leucémie de l'Enfant et de l'Adolescent'), was initiated in 2003 and included all children treated since 1980 in two French regions (west PACA-Corse and Lorraine). Details of the whole programme have been previously described elsewhere.[15] Patients were eligible for this study if they met all the following inclusion criteria: (1) Having undergone HSCT for childhood acute leukaemia after a myeloablative conditioning regimen, (2) Having reached 18 years of age and having achieved FH at the time of inclusion, (3) Having not yet entered adolescence at the time of

transplantation (that is, being younger than 9 years at transplant for girls or 11 years for boys) and being prepubertal (SMR stage 1, according to Marshall and Tanner[16,17]). The age threshold of this third criterion was set 1 year before the average age of acceleration in height velocity,[18] to restrict this study to patients transplanted before the usual time for peripubertal growth spurt. This way, all our patients had a complete evaluation of growth during this peripubertal period.

Fifty-eight young adults met these inclusion criteria and are described here. Among them, 42 had received TBI as part of their conditioning regimen, whereas 16 were prepared with a BU-based conditioning regimen.

Preparative regimens

The preparative regimen depended on the protocols in use at the time of transplantation, the underlying disease and its status, and the existence or not of previous central nervous system (CNS) irradiation. TBI was always administered fractionated, using a 60-cobalt source. All patients received the same total dose of 12 Gy (that is, 2 Gy twice daily during 3 days), with lung shielding at 8 Gy. TBI was associated with CY for 10 patients, to melphalan for 2, to cytarabine and melphalan (TAM regimen, according to Bordigoni *et al*.[19]) for 28 and to thiotepa and melphalan for 2. BU was given per os in 16 divided doses (four doses per day during 4 days) for a total dose of 16 mg/kg or 480 mg/m^2. When prepared with BU, patients received also CY (11 patients), CY plus cytarabine (1 patient) or melphalan (4 patients).

Height growth evaluation

Height was measured at transplantation and then annually until 18 years of age or more, as part of medical examination. Standing height, measured using a Harpenden stadiometer, was used for all patients. Height was expressed as standard deviation score (SDS). Height SDS was calculated using French references,[18] as patient height minus mean height for age and sex, divided by s.d. of height for age and sex. Patients' height SDS were compared at three key periods: at HSCT, at 9 years of age for girls and 11 for boys (9/11 years) and at achievement of FH. FH was defined as the tallest height measured when the patient's age was 18 years or older, and when height velocity was inferior to 1 cm per year. Height at 9/11 years will also be referred to as 'height before the onset of adolescence'. Growth during adolescence was assessed using cumulative change in height, calculated as FH SDS minus 9/11 years height SDS. If negative, it revealed a decrease in height SDS between 9/11 years and FH. If positive, it meant an increase in height SDS between 9/11 years and FH. We also measured change in height SDS from HSCT to onset of adolescence and from HSCT to FH using the same methodology.

Growth hormone (GH) deficiency was detected by measuring insulin-like growth factor I plasma levels and GH peak response to at least two stimulation tests per patient. These tests were insulin tolerance tests (0.05 UI/kg i.v.), GH-releasing hormone infusion tests (80 µg, Somatoreline i.v., Choay/Sanofi, Gentilly, France) or propanolol-glucagon tests (0.25 mg/kg oral propanolol and 1 mg glucagon IM). GH insufficiency was diagnosed when peak GH levels after stimulation were inferior to 20 mUI/l (or 10 ng/ml). The tests were performed at least 6 months away from any antileukaemic treatment. We did not use priming with sex hormones before these tests.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± s.e. Fisher and χ^2 tests were used to compare qualitative variables (demographical and clinical), when Mann–Whitney non-parametric tests were used for all quantitative variables. Multiple linear models were used to construct models of association of either the change in height during adolescence, the change in height from HSCT to FH or the FH SDS (as the dependant variable), with the conditioning regimen (TBI vs BU) as the explanatory variable. Potential confounding factors were gender, age at HSCT, previous CNS irradiation, remission status at HSCT (first CR vs more advanced disease) and type of HSCT (auto- vs allograft). Each model was given with its non-standardized β-coefficient and significance of the association set as $P<0.05$.

Results

Patient characteristics

All patients. Patient characteristics are shown in Table 1. Forty-one patients were transplanted for ALL, whereas 17 suffered from AML. Before transplantation, seven patients had received either prophylactic or curative CNS irradiation. It was cranial irradiation for five patients and craniospinal irradiation for two patients (one patient in each treatment group), with a dose of 18 Gy for six of them and 21 Gy for one patient. Eight boys had received testicular irradiation.

Most patients (32) were in first CR at HSCT, whereas 24 were in second CR and 2 patients had achieved third CR. HSCT was allogeneic for 33 children and autologous for 25 children. After allogeneic transplantation, 20 patients (60.6%) suffered from acute GVHD grades 2–4, and eight patients (24.2%) from chronic GVHD. The mean time from HSCT to last examination was 13.1 years (± 0.5) with a minimum of 7.6 years.

Distribution according to treatment groups (TBI or BU). There was no significant difference between the two groups in terms of gender, age at HSCT, history of CNS or testicular irradiation, type of HSCT or incidence of GVHD (Table 1). As expected, a majority of patients in the TBI group had ALL (38 of 42), whereas most BU patients had AML (13 of 16). First CR at transplantation was also more frequent in the BU group (13 patients of 16) than in the TBI group (19 of 42).

Distribution of GH deficiency and hypothyroidism showed no statistical difference in the two groups, while gonadal side effects were significantly more frequent in the

Table 1 Patient characteristics

	All patients	*TBI group*	*BU group*	P-*value*
No. of patients	58	42	16	
Gender (no. (%))				
Male	40 (69)	28 (66.7)	12 (75)	0.75
Female	18 (31)	14 (33.3)	4 (25)	
Age at inclusion (years, mean ± s.e.)	19.6 ± 0.4	19.3 ± 0.4	20.3 ± 0.9	0.58
Age at diagnosis (years, mean ± s.e.)	5.1 ± 0.3	5.0 ± 0.4	5.3 ± 0.7	0.70
Leukaemia type (no. (%))				
ALL	41 (70.7)	38 (90.5)	3 (18.8)	**<0.001**
AML	17 (29.3)	4 (9.5)	13 (81.2)	
Previous irradiation (no. (%))				
Testicular (no. (% of boys))	8 (20)	4 (14.3)	4 (33.3)	0.21
Cranial (no. (%))	7 (12.1)	3 (7.1)	4 (25)	0.08
Age at HSCT (years, mean ± s.e.)	6.4 ± 0.3	6.6 ± 0.4	5.9 ± 0.7	0.43
Remission status at HSCT (no. (%))				
CR1	32 (55.2)	19 (45.2)	13 (81.3)	**0.049**
CR2	24 (41.4)	21 (50)	3 (18.8)	
CR3	2 (3.5)	2 (4.9)	0	
Type of HSCT (no. (%))				
Autologous	25 (43.1)	19 (45.2)	6 (37.5)	0.60
Allogeneic	33 (56.9)	23 (54.8)	10 (62.5)	
Acute GVHD (grades 2–4) (no. (% of allogeneic recipients))	20 (60.6)	15 (65.2)	5 (50)	0.46
Chronic GVHD (no. (% of allogeneic recipients))	8 (24.2)	7 (30.4)	1 (10)	0.38
Endocrine late effects (no. (%))				
GH deficiency	15 (25.9)	13 (30.9)	2 (12.5)	0.19
GH therapy	13 (22.4)	12 (28.6)	1 (6.2)	0.09
Hypergonadotrophic hypogonadism[a]	33 (56.9)	28 (66.7)	5 (31.2)	0.01
Sex hormone replacement therapy	23 (39.7)	19 (45.2)	4 (25)	0.16
Hypothyroidism[b]	12 (20.7)	11 (26.2)	1 (6.3)	0.15
Hypothyroidism treated	12 (20.7)	11 (26.2)	1 (6.3)	0.15
Time from HSCT to last visit (years, mean ± s.e.)	13.1 ± 0.5	12.6 ± 0.5	14.5 ± 0.9	0.09

Abbreviations: CR1 = first CR; CR2 = second CR; GH = growth hormone; HSCT = haematopoietic SCT.
[a]Defined as high follicle-stimulating hormone and luteinising hormone levels with low oestradiol in women or low testosterone in men.
[b]Defined by a non-transient elevation of thyroid-stimulating hormone.
Bold values indicate *P*-values that are significant ($P<0.05$).

TBI group (28 patients of 42) than in the BU group (5 of 16). None of our patients developed adrenal insufficiency.

Growth assessment

All patients. Overall mean height was near normal at transplantation (mean height SDS: 0.2 ± 0.1) and before the onset of adolescence (mean height SDS at 9/11 years: −0.2 ± 0.1). However, it clearly decreased at achievement of FH with a mean FH SDS at −1.6 ± 0.1. The mean cumulative change in height SDS from HSCT to FH was −1.8 ± 0.1. It was −0.4 ± 0.1 from HSCT to 9/11 years, and −1.4 ± 0.1 during adolescence.

Comparison of growth according to treatment groups. Figure 1 illustrates the evolution of the mean height SDS from HSCT to attainment of FH according to the conditioning regimen. Mean height SDS in the TBI group and in the BU group were not statistically different at HSCT (0.2 ± 0.1 and 0.3 ± 0.2, respectively) and before the onset of adolescence (−0.2 ± 0.1 and −0.1 ± 0.2, respectively). FH was significantly shorter in the TBI group than in the BU group with SDS at −1.8 ± 0.2 vs −0.8 ± 0.2, respectively ($P=0.001$).

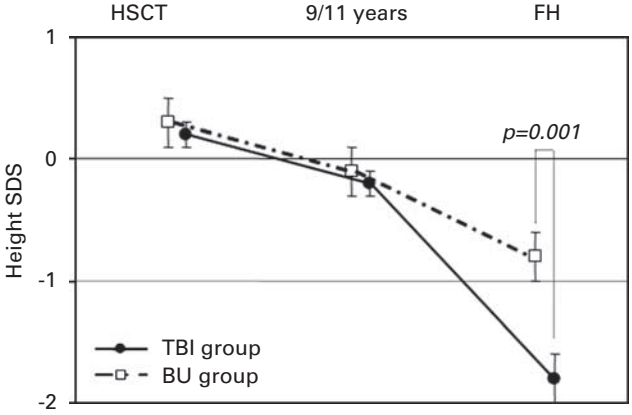

Figure 1 Mean height standard deviation score (SDS) ± s.e. over time by conditioning regimen. Mean final height SDS was significantly lower in the TBI group when compared to the BU group ($P=0.001$).

Loss in height SDS between HSCT and FH was more important after TBI (−2.0 ± 0.2) than after BU (−1.1 ± 0.2,

Table 2 Factors influencing change in height SDS during adolescence and from HSCT to final height (multiple linear regression analysis)

	Mean change in height SDS during adolescence ± s.e.	*Linear regression models*		*Mean change in height SDS from HSCT to FH ± s.e.*	*Linear regression models*	
		β-*coefficient*	P-*value*		β-*coefficient*	P-*value*
Conditioning regimen						
TBI	−1.6 ± 0.1	0.92	**0.003**	−2.0 ± 0.1	0.98	**0.004**
BU	−0.7. ± 0.2			−1.1 ± 0.2		
Gender						
Male	−1.5 ± 0.2	0.36	0.18	−1.8 ± 0.2	0.34	0.25
Female	−1.2 ± 0.2			−1.7 ± 0.2		
CNS irradiation						
Yes	−1.6 ± 0.3	0.61	0.12	−1.9 ± 0.3	0.49	0.27
No	−1.4 ± 0.1			−1.8 ± 0.1		
Age at HSCT, years	NA	−0.02	0.73	NA	0.03	0.59
Remission status at HSCT						
CR1	−1.1 ± 0.2	−0.26	0.32	−1.5 ± 0.2	−0.38	0.18
⩾CR2	−1.7 ± 0.2			−2.1 ± 0.2		
Type of HSCT						
Autologous	−1.3 ± 0.2	−0.34	0.18	−1.7 ± 0.2	−0.3	0.27
Allogeneic	−1.4 ± 0.2			−1.8 ± 0.2		

Abbreviations: CNS = central nervous system; FH = final height; HSCT = haematopoietic SCT; NA = not applicable; SDS = standard deviation score.
Bold values indicate *P*-values that are significant ($P < 0.05$).

$P = 0.002$). From HSCT to 9/11 years, mean height SDS decreased slightly and similarly (-0.4 ± 0.1 in both groups). On the contrary, the decrease in height SDS during adolescence was significantly more pronounced in the TBI group than in the BU group (-1.6 ± 0.1 vs -0.7 ± 0.2, $P = 0.003$).

When excluding patients with CNS irradiation from the BU group, mean FH SDS in this group was -0.7 ± 0.2. Cumulative changes in height SDS were at -1.1 ± 0.2 from HSCT to FH, and at -0.8 ± 0.1 during adolescence.

In the multivariate analyses, the preparative regimen (TBI vs BU) was the only covariate significantly associated with a greater change in height SDS during adolescence and a greater change in height SDS between HSCT and FH (Table 2), but also with a shorter FH ($P = 0.007$).

Discussion

Haematopoietic SCT has long been known to alter height growth and puberty. Nevertheless, very few post transplant studies have focused on growth during the pubertal period.[11–14] In this study, all 58 patients had attained FH at the time of inclusion, and were young enough at HSCT to proceed to a complete assessment of peripubertal growth post transplantation. Our findings underline the crucial role played by post-HSCT alterations of the peripubertal growth spurt in reducing final adult height.

Clement-De Boers *et al*.[11] described a cohort of 16 patients engrafted in their childhood for haematological malignancies. Prepubertal growth velocity was not altered, whereas pubertal height gain was severely reduced when compared to reference data. Bakker *et al*.[14] reported similar alterations of the peripubertal growth spurt when measuring peak height velocity of 43 children transplanted before the onset of puberty. In another study,[12] 18 prepubertal children at the time of HSCT also showed a decrease in height SDS from onset of puberty to FH (mean cumulative change: −0.9). Frisk *et al*.[13] studied height growth of 17 patients with ALL treated with autologous HSCT. Decrease in height SDS between the last prepubertal examination and FH was significant, whereas prepubertal change in height SDS was not. It is noteworthy that these four studies described only patients receiving TBI and could not evaluate the impact of BU-based conditioning regimens on pubertal growth. Furthermore, pubertal growth was studied from the onset of puberty, defined according to Tanner's puberty stages. However, after HCST, patients often have puberty disorders because of their gonadal dysfunction and puberty stages might be altered as a consequence of HSCT or of hormonal therapy. As a result, the age at the onset of puberty varies greatly and depends on treatments. In our study, we chose to set the intermediate evaluation time (height at 9/11 years) before the average normal time for acceleration of growth in healthy children. For paediatricians, these age thresholds should correspond to the onset of a period of intensified monitoring of height growth.

Moreover, surveillance must be prolonged until adult age, whether patients were prepared for HSCT with a TBI- or BU-based conditioning regimen. Indeed, our results confirm that post-HSCT growth is severely impaired, as in previous studies on children transplanted with TBI before the onset of puberty,[11–14,20] but also reveals that high-dose BU has a negative impact on height growth with a mean decrease in height SDS from HSCT to FH at -1.1 ± 0.2. This effect of BU on growth was suggested by Bakker *et al*.[21] They found unexplained post transplant alteration of growth patterns in 35% of the children without growth-limiting disorders. Yet, probably due to limited follow-up (median 6 years) and

heterogeneity of previous diagnoses, they failed to show a significant decrease in height SDS. Similarly, previous studies[6,20,22–24] had not detected altered growth in children prepared with BU. In most studies,[6,22–24] children had not attained FH at inclusion and growth was studied only during the first years of post transplantation. In another study,[20] among 181 children treated with HSCT for various pathologies, 36 had not received irradiation. The change in height SDS between HSCT and FH in non-irradiated patients was only −0.07. Nevertheless, among them, 26 patients had received only CY for severe aplastic anaemia, and only 10 patients were prepared with BU and CY. Their mean age at HSCT was older (11.7 years) than in our cohort (5.9 years). As a result, the period of height follow-up was shorter and could not thoroughly cover potential effects of BU on pubertal growth spurts. It could be argued that our results in the BU group are worsened by previous CNS irradiation in four patients. However, even when excluding these four patients, results were similar. BU is a drug highly toxic for gonads. Impaired gonadal function is known to alter peripubertal growth, through dysregulation of interactions between sex hormones and GH.[10] This provides potential explanations for the adverse effects of BU on growth observed in our cohort.

This study also underlines that TBI causes more profound impairment of growth than a BU-based conditioning regimen. The differences observed between the two patient groups appeared after the onset of adolescence. This could be attributed to complex interlinked mechanisms implying GH deficiency but also direct damage induced on epiphyseal cartilage[5,7,10] (altering bone growth) and gonads.[7,10] Some authors have shown that fractionated TBI is less toxic than single fraction.[25] However, recent reports underlined that fractionated TBI still leads to major reduction of FH.[9,14,26] Our results confirm that the use of TBI still causes more damage on growth than non-TBI containing regimen, even in the context of a 3-day and 6-doses fractionated irradiation.

Because this study is retrospective, we cannot completely rule out potential bias in our comparison of TBI vs BU. Several authors have reported that age at transplantation and previous CNS irradiation were risk factors for post transplant height growth failure. Allogeneic transplantation is also expected to be at high risk for growth due to incidence of GVHD and consecutive requirement for prolonged steroid therapy. Noteworthy, the difference shown between TBI and BU patients remained statistically significant in multivariate analyses after adjusting for these potential confounders. It could also be argued that this study does not report the natural history of height growth after transplantation with either TBI or BU because a substantial proportion of children received GH and/or thyroxin therapy. Yet, these therapies appeared to be more frequently used in the TBI than in the BU group. As a result, the difference between the two groups might be even greater without these treatments.

In conclusion, this study confirms the need for a prolonged and careful monitoring of height growth after HSCT for childhood leukaemia. Surveillance must be intensified during the whole period of adolescence. Clinicians and patients must be aware that preparations involving high-dose BU, although less toxic than TBI-containing regimen, might also have adverse effects on height growth during adolescence and on FH.

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