Growth hormone treatment of growth failure secondary to total body irradiation and bone marrow transplantation

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Abstract

Growth hormone was given to 13 children (nine boys, four girls) with acute leukaemia who had undergone treatment with cyclophosphamide and total body irradiation before bone marrow transplantation. Mean age at total body irradiation and bone marrow transplantation was 9·0 years (range 3·7–15·8). Endocrinological investigation was carried out at a mean of 2·0 years (range 0·4–4·0) after bone marrow transplantation. Peak serum growth hormone responses to hypoglycaemia were <10·0 µg/l (<20·0 mU/l) in 10, 10·5 µg/l (21·0 mU/l) in one, >16·0 µg/l (>32·0 mU/l) in two patients. Mean age of the patients at the start of growth hormone treatment was 12·2 years (range 5·8–18·2). The mean time between total body irradiation and bone marrow transplantation and the start of growth hormone treatment was 3·2 years (range, 1·1–5·0). Height velocity SD score (SD) increased from a mean pretreatment value of −1·27 (0·65) to + 0·22 (0·81) in the first year, +0·16 (1·11) in the second year, and +0·42 (0·71) in the third year of treatment. Height SD score (SD) changed only slightly from −1·52 (0·42) to −1·50 (0·47) in the first year, to −1·50 (0·46) in the second year, and −1·74 (0·92) in the third year. Measurement of segmental proportions showed no significant increase in subischial leg length from −0·87 (0·67) to −0·63 (0·65) in the first year, to −0·58 (0·70) in the second year, and −0·80 (1·14) in the third year of treatment.

Our data indicate that children who have undergone total body irradiation and bone marrow transplantation respond to treatment with growth hormone in either of two dose regimens, with an increase in height velocity that is adequate to restore a normal growth rate but not to 'catch up', and that total body irradiation impairs not only spinal but also leg growth, possibly by a direct effect of irradiation on the epiphyses and soft tissues.

The introduction of high dose chemotherapy and radiotherapy with bone marrow transplantation to the armamentarium of treatments against malignant disease has made cure possible for a substantial number of children who would, hitherto, not have survived.[1] The high dose chemotherapy and total body irradiation that are used for conditioning such patients before bone marrow transplantation do, however, cause considerable morbidity; cataract formation,[1] gonadal failure, hypothyroidism, and growth failure have all been reported.[2][3] It

has been suggested that total body irradiation impairs spinal growth,[2] and causes growth hormone insufficiency.[2][3] We have reported a 59% incidence of growth hormone insufficiency in children after bone marrow transplantation, some of whom had received cranial irradiation.[2] A high incidence of growth hormone insufficiency in children treated with total body irradiation has also been reported by Sanders *et al*.[3]

Children who have growth hormone insufficiency as a result of either cranial or craniospinal irradiation have an initial 'catch up' phase of growth in response to treatment with growth hormone, although it is less pronounced than that of children with idiopathic growth hormone deficiency.[4-7] This may be explained by the longer time for which children with congenital growth hormone deficiency have impaired growth hormone secretion, but all authors are agreed that both groups have a faster than normal growth rate (catch up) after starting growth hormone treatment.[4-7] We have analysed the short term effect of growth hormone treatment in 13 children treated with cyclosphosphamide, total body irradiation, and bone marrow transplantation for acute leukaemia.

Patients and methods

Thirteen patients (nine boys, four girls) who underwent bone marrow transplantation and total body irradiation for acute leukaemia and then received growth hormone treatment were included in this study. All had abnormal growth rates for their chronological age or stage of puberty, or both. The diagnosis was acute lymphoblastic leukaemia in 11 and acute myeloid leukaemia in two. Mean age at diagnosis was 6·5 years (range 0·5–14·1). All patients with lymphoblastic leukaemia had been treated for varying times with protocols established by the Medical Research Council,[8] the United Kingdom Children's Cancer Study Group,[9] or by the Hospital for Sick Children.[10] Patients with myeloid leukaemia were treated with daunorubicin, cytosine arabinoside, and thioguananine, or with two courses of this before one course of meta-amsacrine, azacytidine, and etoposide VP16 together with intrathecal cytosine arabinoside. Eight of those with lymphoblastic leukaemia had previously undergone cranial irradiation for the prevention of meningeal leukaemic infiltration in a dose of 1800 cGy (n=3) in 10 fractions over 12 days or 2400 cGy (n=5) in 15 fractions over 19 days. All the children with lymphoblastic disease also received intrathecal methotrexate. Eight patients had

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relapsed and were therefore given additional induction and consolidation chemotherapy before bone marrow transplantation. One boy (case 7) was also given treatment for testicular relapse with 2400 cGy testicular irradiation.

Allogeneic bone marrow transplantation was done during the first remission in five, the second remission in five, and the third remission in two patients. One patient underwent autologous bone marrow transplantation during the second remission after central nervous system relapse. Mean age at the time of treatment was 9·0 years (range 3·7–15·8). Preparation for marrow transplantation consisted of cyclophosphamide 60 mg/kg/day intravenously over two consecutive days and total body irradiation. The dose of irradiation was 900–1000 cGy given as a single fraction in 12 patients and in six fractions over three days in one.

A mean of 3·2 years (range 1·1–5·0) elapsed between irradiation and transplantation and the start of growth hormone treatment. The table gives the clinical data of 13 patients at the start of growth hormone treatment. The mean age of starting growth hormone treatment was 12·2 years (range 5·8–18·2). Endocrine replacement treatment was a standard regimen of hydrocortisone 15 mg/m²/day in two divided doses and thyroxine 100 µg/m²/day. Human growth hormone treatment was started at a mean dose of 13·0 U/m²/week by daily subcutaneous injections and increased to a mean of 18 U/m²/week in the second and third years. Two patients (cases 9 and 13) had graft versus host disease, but only one (case 13) remained on steroid treatment while taking growth hormone. Statistical analysis was by paired Student's t test.

The endocrine status of all patients was assessed at a mean of 2·0 years (range 0·6–4·0) after total body irradiation and bone marrow transplantation. The hypothalamopituitary axis was tested with a combined provocative test using insulin, luteinising hormone releasing hormone, and thyrotrophin releasing hormone by standard techniques.[11] In four patients in whom growth hormone responded inadequately to hypoglycaemia (peak <10·0 µg/l (<20·0 mU/l)), a growth hormone releasing hormone test was done. Basal serum concentrations were also measured. After endocrine assessment patients were followed up clinically at three to six month

intervals and repeat hormone measurements were made as necessary. Anthropometric measurements including standing and sitting height were assessed with stadiometers by standard techniques.[12] Pubertal stages were assessed by the method of Tanner.[13] Testicular volume after irradiation (localised irradiation as well as a component of total body irradiation) is an unreliable index of sexual maturity, so genital appearance was used.[14] Growth standards were those of Tanner *et al.*[15]

Results

ENDOCRINOLOGICAL INVESTIGATIONS

Serum growth hormone response to insulin induced hypoglycaemia was <10·0 µg/l (<20·0 mU/l) in 10 patients, six of whom had concentrations ≤5·0 µg/l (≤10·0 mU/l). One patient had a peak growth hormone of 10·5 µg/l (21·0 mU/l) and two had peak concentrations of >16·0 µg/l (>32·0 mU/l) (both had low growth velocities). Eight of the 10 patients with growth hormone insufficiency had been treated with cranial irradiation. Five out of the six patients with growth hormone concentrations <5·0 µg/l (<10·0 mU/l) had been treated with cranial irradiation (table). Only one of the four children who were tested with growth hormone releasing hormone had growth hormone concentrations higher than those achieved during insulin
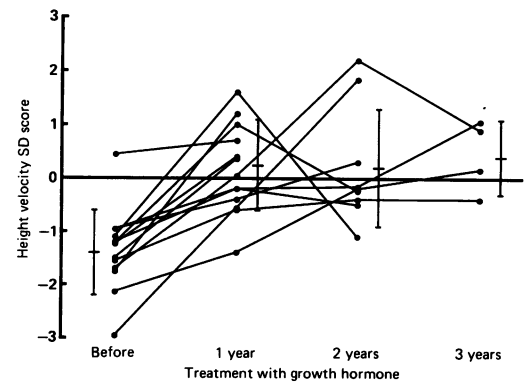

Figure 1   Height velocity SD scores at the beginning of growth hormone treatment, after 1 year (13 U/m²/week), and 2 and 3 years (18 U/m²/week) of growth hormone treatment in 13 children treated by total body irradiation and bone marrow transplantation.

Clinical and endocrine data of 13 patients treated with total body irradiation and bone marrow transplantation at the beginning of growth hormone treatment

Case No	Sex	Previous cranial irradiation and dose (cGy)	Age at total body irradiation/bone marrow transplantation (years)	Growth hormone peak to hypoglycaemia (µg/l)*	Pubertal stage genitalia/breast	Endocrine replacement treatment
1	M	2400	10·1	4·8	2	Nil
2	M	1800	5·4	7·5	1	Nil
3	M	1800	15·8	<0·3	4	Thyroxine
4	M	2400	5·1	5·0	1	Nil
5	F	Nil	6·5	9·9	1	Nil
6	F	2400	8·3	9·2	2	Oestrogen
7	M	2400 (2400 to testes)	11·1	1·1	1	Thyroxine, hydrocortisone
8	M	2400	9·8	5·6	4	Nil
9	M	Nil	12·2	10·5	3	Nil
10	F	Nil	9·7	>16·0	3	Oestrogen
11	M	Nil	12·0	>16·0	3	Thyroxine, testosterone
12	F	1800	3·7	3·3	1	Nil
13	M	Nil	7·3	4·5	1	Thyroxine, hydrocortisone

All patients had acute lymphoblastic leukaemia except numbers 5 and 11 who had acute myeloid leukaemia.
*Growth hormone conversion: 1 µg/l=2 mU/l.

induced hypoglycaemia, but none achieved values >10·0 µg/l (>20·0 mU/l).

Four patients were hypothyroid (cases 3, 7, 11, and 13) at the time of the initial investigation, case 2 had compensated hypothyroidism identified by persistently raised concentrations
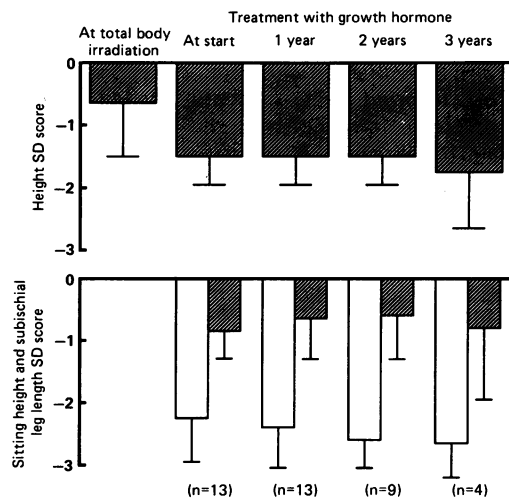

Figure 2   Height, sitting height, and subischial leg length (shaded columns) SD scores before and during growth hormone treatment in 13 children treated by total body irradiation and bone marrow transplantation.

of thyroid stimulating hormone (>10·0 mU/l). All four were treated with thyroxine as were two patients (cases 1 and 8) who became hypothyroid 3·7 and 2·5 years later, respectively. Adrenal function was considered normal in all patients except two (cases 7 and 13), who subsequently received hydrocortisone replacement for panhypopituitarism. During the study, sex steroid replacements were given to six patients. Three patients (cases 6, 7, and 10) had increased serum concentrations of follicle stimulating hormone and luteinising hormone on investigation; two (cases 1 and 8) had arrested pubertal development and one (case 13) delayed puberty. Patients less than 10 years of age at investigation did not have raised gonadotrophin concentrations, although at this age it is impossible to exclude gonadal damage by measurement of serum gonadotrophins.

GROWTH IN RESPONSE TO TREATMENT WITH GROWTH HORMONE

In the first year of growth hormone treatment all patients increased their growth velocity, expressed as height velocity SD score (SD), from a mean of −1·27 (0·65) in the year before treatment to +0·22 (0·81), (p<0·001) (fig 1). During the second year of treatment the mean height velocity SD score was +0·16 (1·11) and during the third year it was 0·42 (0·71). Height velocity SD score did not rise significantly above zero in any year of treatment, showing that these patients did not experience 'catch up' growth. Expressing growth velocity in cm/year (SD) in the first year of treatment, patients increased their height velocity from a mean value in the year before treatment of 3·6 (0·95) cm/yr to 5·2 (1·5), whereas in the second year it decreased to a mean of 5·0 (2·5) cm/year, and in the third year to 4·6 (2·0) cm/year.

Mean height SD score at the time of bone marrow transplantation was −0·66 (0·84) and when growth hormone treatment started it decreased to −1·52 (0·42) (p<0·05). Growth hormone treatment did not result in improvement of height SD scores (fig 2); during the first year there was a slight increase to a mean value of −1·50 (0·47), which was maintained in the second year at −1·5 (0·46), and then decreased to −1·74 (0·92) in the third year.

The response of body segments to growth hormone treatment are shown in fig 2. At the start of growth hormone treatment, sitting height SD scores (SD) had been affected more than subischial leg length, with a mean value of −2·26 (0·68) and −0·87 (0·63), respectively. During treatment there was a progressive, although not significant, decrease in mean sitting height SD scores, from −2·46 (0·64) in the first year, to −2·60 (0·50) in the second year, and −2·66 (0·59) in the third year. The response of subischial leg length to growth hormone treatment was also not significant: in the first year mean subischial leg length SD score was −0·63 (0·65), in the second year −0·58 (0·70), and in the third year −0·8 (1·14). An example of impaired sitting height and subischial leg length responses to growth hormone treatment is shown in fig 3 (case 1).
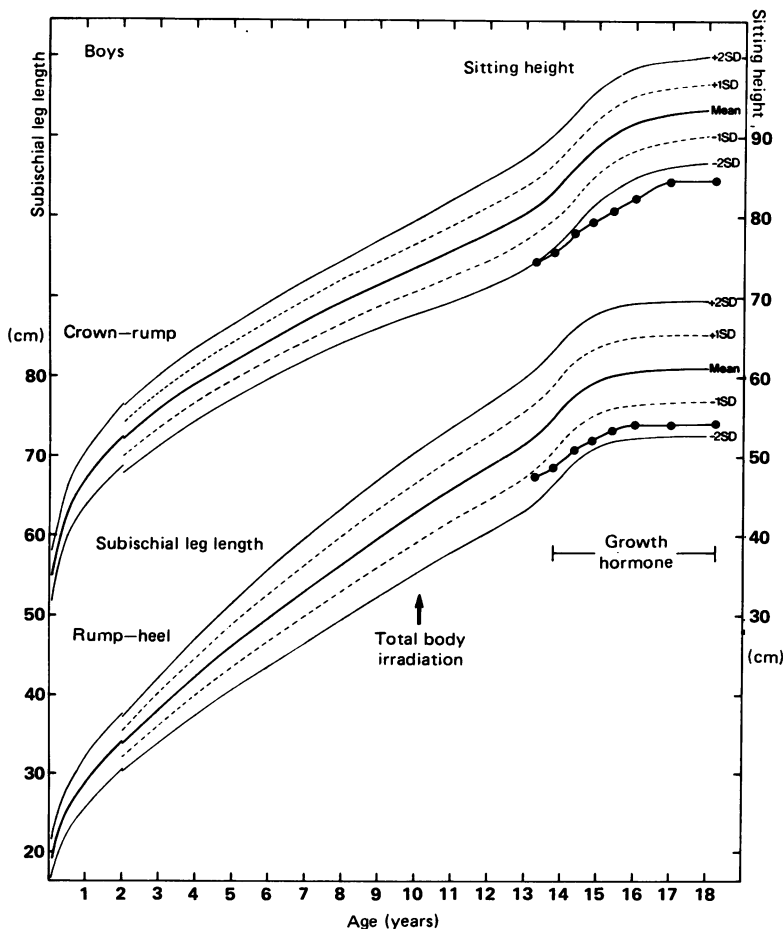

Figure 3   Sitting height and subischial leg length response to treatment with growth hormone in case 1 until the attainment of adult stature. Epiphyseal maturation was one year behind chronological age at the start of treatment. He had been treated with 2400 cGy cranial irradiation at the age of 3·8 years and total body irradiation was given at the age of 10·1 years. He had spontaneous onset of pubertal development at age of 13·2 years but sex steroid supplements were given at the age of 15·1 years for arrested sexual maturation.

Discussion

The patients in this study are a heterogenous group because of their wide age range, differing pubertal state, and varying numbers of previous remissions and irradiation regimens. They were, however, treated at a time when total body irradiation and bone marrow transplantation were first used in our unit, and before this such children would not have been expected to survive. Growth assessment and potential may be complicated by chronic corticosteroid treatment in those patients with severe graft versus host disease, but only one of our patients was on pharmacological corticosteroid treatment during growth hormone treatment. We have previously shown that growth hormone insufficiency is a common result of total body irradiation and this is especially true for children who have been treated with bone marrow transplantation during their second or third remission and have already received cranial irradiation.[2] We can offer no explanation as to why sitting height SD scores were much lower than sub-ischial leg length SD scores before growth hormone treatment.

Children who do not produce enough growth hormone as a result of cranial or craniospinal irradiation have been reported to respond to growth hormone treatment with an initial catch up growth period, although this is not as pronounced as in those children with idiopathic growth hormone deficiency.[4-7] In this study patients showed an increase in height velocity adequate for growth at a normal rate for age (height SD scores increased from a minus number to zero), but this was not catch up growth (height SD scores were not significantly above zero). Children with idiopathic growth hormone deficiency have catch up growth in response to growth hormone treatment with doses similar to that used in the first year for our patients.[16] We provided a higher dose in the second and third years but with no further improvement in growth response. It is possible that higher doses of growth hormone, such as those used now in the treatment of dysmorphic syndromes (30 U/m²/week), may be needed for optimal growth of such children.

Impaired spinal growth despite growth hormone treatment was expected in our patients, as growth hormone does not reverse impaired growth of the spine in children who have undergone craniospinal irradiation.[17] It was recently reported that children treated with only cranial irradiation also had abnormal unexplained spinal growth, but the data are from a small number of patients.[18] The patients in our study had impaired leg growth while on growth hormone treatment even though they received full endocrine replacement, suggesting that total body irradiation impaired the growth of both lower limb and vertebral epiphyses. Irradiation of the bones of the legs impairs the growth of the lower limbs,[19 20] just as spinal irradiation affects the growth of the vertebral bodies.[21] As growth failure in these children was more pronounced than expected for such a low total dose of irra-

diation, it may be attributable to the effect of total body irradiation given as a single fraction in almost all the patients. It is possible that fractionation of the dose will decrease the adverse effects on growth as well as other complications.

Children treated with total body irradiation and bone marrow transplantation have profound growth failure, which is only partially the result of endocrine deficiency. They have impaired response to growth hormone treatment in the lower segment of the body as well as in the spine, which is probably secondary to irradiation of the epiphyses. Such damage may be irreversible and this emphasises that children who have been treated with total body irradiation and have growth failure require endocrine replacement as soon as possible to maximise their impaired growth potential.

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