Growth in Children After Bone Marrow Transplantation for Acute Leukemia

By Zilla Huma, Farid Boulad, Patricia Black, Glenn Heller, and Charles Sklar

We evaluated the growth of children with acute leukemia who received a bone marrow transplant (BMT) after preparation with hyperfractionated total body irradiation (TBI). Seventy-two patients (27 female and 45 male patients) with acute lymphoblastic leukemia (ALL; n = 39) or acute myelogenous leukemia (AML; n = 33) who were less than 14 years of age at BMT were studied. Before BMT all had received multagent chemotherapy and 31 had received cranial irradiation (RT). Preparation for BMT included total body irradiation (RT) before transplant with doses of 1,000 cGy (n = 31), 1,500 cGy (n = 37), or 1,500 cGy (n = 35). Heights, expressed as standard deviation scores (SDS), were studied up to 4 years post-BMT. The estimated height SDS for the entire group at the time of BMT was -0.28 ± 0.05 and decreased to -1.11 ± 0.22 at 4 years post-BMT (P < .0001). Using a growth curve model to compare covariate groups over the period of study, we found that the loss in height SDS was most significant in those patients who received cranial RT before BMT (P = .005). The estimated height SDS for patients treated with cranial RT went from -0.52 ± 0.20 at transplantation to -1.83 ± 0.23 4 years later. In contrast, patients who did not receive cranial RT before BMT showed a smaller decrease in height SDS over the 4-year observation period, ie, -0.11 ± 0.20 decreasing to -0.73 ± 0.21. Similarly, patients with a diagnosis of ALL had a greater loss of height SDS than those with AML (P = .03). Fifteen of 18 patients tested were found to be growth hormone (GH) deficient; 9 patients were treated with GH and all showed an improvement in growth velocity (P < .0001). We conclude that (1) children with acute leukemia who have received cranial RT and subsequently undergo BMT, primarily those with ALL, are at high risk for growth failure and GH deficiency, and (2) that fractionation of TBI may have a relative sparing effect on growth.

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Sixty-six patients received an allogeneic marrow transplant. Fifty-three of these patients received an unmodified marrow transplant, whereas 13 patients received a T-cell—depleted transplant. Six patients received an autologous marrow transplant. These procedures have been described previously.\(^3,4\) GVHD prophylaxis in the patients who received an unmodified BMT consisted of methotrexate (MTX) either alone (n = 36) or with steroids (n = 2), cyclosporin A (CSA) either alone (n = 2) or with steroids (n = 2), or the combination of CSA and MTX (n = 11).

GVHD. Acute GVHD occurred in 10 patients. Chronic GVHD was diagnosed according to the criteria of Shulman et al.\(^1\) Of the 66 evaluable patients who received allogeneic BMT, 15 had chronic GVHD posttransplant. Eleven of these 15 patients had a mild or localized form of the disease, and 4 patients had extensive chronic GVHD. Treatment of chronic GVHD was as follows. Seven patients received azathioprine and steroids (prednisone at 1 to 2 mg/kg/d), 4 patients received azathioprine alone, 1 patient received only steroids, and 3 patients did not require treatment. The duration of steroid therapy was 6 to greater than 120 months, and azathioprine was used for 12 to greater than 120 months.

Growth. All standing heights were measured using a fixed wall-mounted ruler at intervals of 3 to 12 months. Eighteen of these patients who were noted to be growing poorly were evaluated for growth hormone (GH) deficiency by at least two methods; each underwent GH testing with a combination of insulin, L-dopa, or Clonidine. Serum GH was determined using the Quantitope radioimmunoassay kit (Chasted, MN). The intraassay coefficient of variation was 3.5%, the interassay coefficient of variation was 6.5%, and the limit of detection was 0.2 ng/mL. A peak value less than 10 ng/mL was regarded as representing GH deficiency. Patients were treated with recombinant human GH (Humatrope or Protropin at 0.2 to 0.3 mg/kg/wk) as daily or thrice weekly subcutaneous injections.

Statistics. Height determinations were converted to the number of standard deviations (SD) from the age- and sex-adjusted norm to give SD scores (or SDS).\(^1,11\) A child that is average in height will have an SDS of 0. A growth curve model was constructed to examine the relationship between SDS over time and the following covariates: diagnosis, age, sex, total body irradiation, cranial RT, and acute and chronic GVHD. The relationship is expressed through the model: \(Y_i = \mu + t \cdot \beta_1 + \sum_i a_i + X_i \cdot \beta_2 + X_i \cdot \alpha_i + e_i\), where \(Y_i\) represents the SDS for individual i at time t (t = baseline, 1, 2, 3 and 4 years), \(X_i\) is the covariate value for factor j, and e is assumed to be a normally distributed random variable with mean 0 and variance \(\sigma^2\). The parameters \(\beta\) and \(\alpha\) represent the effect of time and covariate on the SDS. The parameter \(\beta_2\) represents the rate of change of SDS over time within covariate j. If \(\beta_2 = 0\), then the slope of SDS over time is the same for each group in covariate j. The parameters in this regression model were estimated by the method of maximum likelihood and the Wald statistic was used to test the equality of growth rates.\(^14\) This model allows the comparison of change in SDS between covariate groups over time. The P values listed in Table 2 refer to a test of whether the rate of change in the SDS over time is different between these groups. For the patients treated with GH, height velocities over a minimum 6-month period were annualized and then converted to give an SDS.\(^15\) Growth velocity SDSs were calculated according to bone age which was determined by the standards of Greulich and Pyle.\(^18\)

## RESULTS

The group as a whole showed a fall-off in growth with no evidence of catch-up growth (Fig 1). The estimated height SDS pretransplant for the entire group (-0.28 ± 0.05) was similar to the general population and decreased to -1.11 ± 0.22 over 4 years. The change in height SDS over this time was significant (\(P < .0001\)). Actual heights were greater than two SD below the mean for 5 of 72 (7%) at BMT, for 7 of 47 patients (15%) at 2 years, and for 6 of 24 patients (25%) at 4 years post-BMT.

Patients treated with cranial RT had a significantly greater decrease in height SDS over the first 4 years after transplantation than those who did not receive cranial RT (\(P = .005\)). Based on our growth curve model, the estimated height SDS for patients treated with cranial RT went from -0.52 ± 0.20 to -1.83 ± 0.23 4 years later (Fig 2). In contrast, the estimated height SDS of those not treated with cranial RT shows a significantly smaller loss, from -0.11 ± 0.20 to -0.73 ± 0.21.

A similar result in the change in height SDS was found for the two diagnostic groups. Patients with ALL had a significantly greater loss in height SDS over the 4-year post-BMT period than those with AML (\(P = .033\)). The estimated height SDS for those with ALL went from -0.39 ± 0.18 at transplant to -1.54 ± 0.20 4 years later. For patients diag-

<table>
<thead>
<tr>
<th>Table 1. Patient and Treatment Parameters at BMT</th>
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<tbody>
<tr>
<td>Total No. of Patients</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
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</tr>
<tr>
<td>Female</td>
</tr>
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<td>Median age at BMT</td>
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<td>CNS RT</td>
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</tr>
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<tr>
<td>No</td>
</tr>
<tr>
<td>Not evaluable</td>
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<tr>
<td>Acute GVHD</td>
</tr>
</tbody>
</table>

The parameter \(\alpha\) represents the rate of change of SDS over time within covariate j. If \(\alpha = 0\), then the slope of SDS over time is the same for each group in covariate j. The parameters in this regression model were estimated by the method of maximum likelihood and the Wald statistic was used to test the equality of growth rates.\(^14\) This model allows the comparison of change in SDS between covariate groups over time. The P values listed in Table 2 refer to a test of whether the rate of change in the SDS over time is different between these groups. For the patients treated with GH, height velocities over a minimum 6-month period were annualized and then converted to give an SDS.\(^15\) Growth velocity SDSs were calculated according to bone age which was determined by the standards of Greulich and Pyle.\(^18\)
nosed with AML, the estimated height SDS went from $-0.14 \pm 0.18$ to $-0.75 \pm 0.18$ (Fig 3).

Unfortunately, because of the strong confounding between cranial RT and diagnosis, it is not possible to separate out their individual effects on height SDS. Among the 39 patients diagnosed with ALL, 25 were treated with cranial RT. Similarly, among the 33 patients diagnosed with AML, only 4 were treated with cranial RT.

We were unable to find a correlation between height SDS after BMT and age at BMT, sex, type of BMT, dose of cranial RT, or dose of TBI (Table 2). In addition, neither the presence of acute or chronic GVHD was significantly correlated with height outcome. However, it is possible that this nonsignificance is due to the small number of episodes of GVHD (acute [$n = 10$] and chronic [$n = 15$]) experienced at our center. Evaluation of change in height SDS based on type of chemotherapy was not possible because five different regimens were used, most used cyclophosphamide, and two overlapped in their use of VP 16. After controlling for either cranial RT or diagnosis, none of the factors described above correlated with height SDS.

Eighteen patients underwent GH testing at a mean of 3.7 $\pm$ 0.6 years post-BMT. Of the patients tested, 12 of 13 who had received cranial RT (ALL [$n = 11$]; AML [$n = 1$]) were found to be GH deficient and 3 of 5 who had not received cranial RT were also deficient (all 3 had AML). Nine of the 15 GH-deficient patients subsequently received GH therapy. Their mean age at initiation of therapy was 12.4 $\pm$ 0.9 years, their mean bone age was 11.7 $\pm$ 0.9 years, their mean growth rate was 2.9 $\pm$ 0.6 cm/yr, and their mean growth velocity SDS before GH treatment was $-2.7 \pm 0.7$. Two of the patients were prepubertal, whereas 7 were in puberty. GH therapy was initiated a mean of 5.2 $\pm$ 0.8 years after BMT. Growth rate after 1 year of therapy was 6.1 $\pm$ 0.9 cm/yr and growth velocity SDS was $+1.2 \pm 0.6$. All patients showed an improvement in their growth velocity SDS after treatment with GH ($P < .0001$; Fig 4).

**DISCUSSION**

Impaired linear growth has been a consistent finding in children after BMT for hematologic malignancies and is most probably due to the interaction of a multitude of factors...
including patient characteristics (e.g., age and sex), treatment variables such as prior cranial RT and type of preparative regimen, and post-treatment complications, principally GVHD. Although certain risk factors have been associated with more severe growth retardation, most patient subgroups appear to have been affected\(^3\,5\,18\) with little evidence of catch-up growth.\(^18\) In particular, conditioning regimens that include TBI appear to result in the greatest loss in height potential.\(^3\,4\,19\)

In a large series reported from Seattle, Sanders et al\(^2\) found that at 5 years posttransplant all of their subjects with leukemia and lymphoma had a height SDS more than 2 SD below the mean.\(^16\) Growth was more impaired in the patients treated with single-dose (920 to 1,000 cGy) compared with those treated with fractionated (200 to 225 cGy/d for 6 to 7 days) TBI and in those with chronic GVHD (incidence, 35%). Further comparison of reports on the growth of children after BMT indicate smaller losses in height potential in those children who received fractionated TBI compared with those treated with single-dose TBI. In patients with acute leukemia treated with single-dose TBI (750 cGy), Bushhouse et al\(^4\) found a decrease of nearly \(-1.5\) in mean height SDS 4 years post-BMT despite a low incidence of chronic GVHD (14%). In contrast, after 2 years of follow-up, Wingard et al\(^5\) found a loss of only 0.3 in median height SDS in 23 patients treated with fractionated TBI (300 cGy/d for 4 days). Similarly, over the first 3 years after BMT, Brauner et al\(^6\) found a mean change of \(-1.4\) in height SDS after single-exposure TBI (1,000 cGy, \(n = 11\)), but a loss of only 0.4 SDS after fractionated TBI (200 cGy twice daily for 3 days, \(n = 6\)); patients with prior cranial RT and those with chronic GVHD were excluded. Thomas et al\(^18\) have also shown a greater loss in height SDS in patients who received single-dose TBI (900 to 1,000 cGy) compared with those who had received fractionated TBI (1,200 to 1,440 cGy in 6 to 8 fractions over 3 days) over a 3-year period.

We have evaluated growth post-BMT in a group of 72 children with acute leukemia after hyperfractionated TBI. Our results showed a mean cumulative change in height SDS of \(-0.83\) for the group as a whole over the first 4 years after BMT, with only 25% of patients attaining a height greater than 2 SD below the mean. The subgroup of patients who did not receive cranial RT before BMT experienced even less growth impairment, confirming the experience of others.

The growth impairment associated with TBI appears to result primarily from direct radiation damage to the epiphyses in the legs and spine.\(^21\,22\) Because the biologic effect of RT is directly related to both the total dose delivered as well as the dose per fraction,\(^23\) it is not surprising that patients treated with fractionated TBI have been shown to grow better than subjects treated with single-dose TBI.\(^16\,17\,19\) Thus, we postulate that the growth sparing observed in our patients is due to, at least in part, the use of fractionation. We cannot exclude the possibility that other factors, especially the relatively low incidence of GVHD (21%) in our series, may have also contributed to these promising results.

In analyzing our data, the only variable associated with
change in height SDS, other than prior cranial RT, was diagnosis. Because these two factors are so confounded, it has not been possible to determine if and to what extent each exerts its own independent effect on growth. Nonetheless, we assume that prior cranial RT is the predominant factor responsible for loss of height SDS, in keeping with the data of others.20-24 The mechanism for the growth failure seen with the use of prior cranial RT is presumed to be damage to the hypothalamic-pituitary region resulting in GH insufficiency.30-31 We found an 80% incidence of GH deficiency in a relatively small group of subjects, most of whom had received prior cranial RT. A variable but high incidence of GH deficiency after TBI has been reported by others, with a greater incidence seen in patients treated initially with cranial RT.30-33

The response to short-term GH therapy was quite gratifying in that all our subjects showed an improvement in their growth velocity SDS, from -2.7 at commencement of therapy to +1.2 1 year later. Papadimitriou et al29 noted normalization of growth (growth velocity SDS score of -1.27 before treatment increasing to +0.22 1 year later), but no catch-up in 13 children and adolescents treated with GH after BMT with single-dose TBI. Thomas et al30 found no significant improvement in height SDS in 24 children treated with GH with no evidence of catch-up growth after 4 years of treatment. Their analysis included prepubertal and postpubertal patients treated with fractionated and single-dose TBI. Although preliminary, our results are suggestive of a potential for catch-up growth over time. Given that the existing data are so limited, it is currently not possible to draw any conclusions on the ultimate value of GH treatment in children surviving BMT.

We conclude that children with acute leukemia who undergo BMT using hyperfractionated TBI experience less severe growth impairment than reported after single-dose TBI. These results support the hypothesis that both total dose and fractionation are critical determinants of height outcome after TBI. Nonetheless, a significant decrease in height SDS and a high incidence of GH deficiency were noted in patients treated with prior cranial RT. The effect of GH therapy on the growth rates of these patients is promising but preliminary and will require validation in patients treated more long term.

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