Growth was assessed during the first and second years following bone marrow transplantation (BMT) in 47 children treated by either busulfan plus cyclophosphamide (BU/CY) \( (n = 24) \) or cyclophosphamide plus fractionated total body irradiation (CY/TBI) \( (n = 23) \). Before transplant, the median height was only 0.2 SD below age- and sex-adjusted means (range, -2.5 to +3.0). Height was greater than 2.0 SD below normal in only three patients (6%). The pretransplant heights were comparable in the BU/CY and CY/TBI groups \( (P = .35) \). Following transplant, median 1- and 2-year heights were 0.7 and 0.9 SD below normal, respectively. Growth rates were 2.2 SD and 1.4 SD below normal during the first and second years, respectively. Growth rates were greater than 2.0 SD below normal in 24 of 47 (51%) at 1 year and in 12 of 31 (39%) at 2 years after transplant. Growth rates in patients treated with BU/CY were comparable to those treated with CY/TBI during both years: 2.5 versus -1.7 SD during the first year \( (P = .19, \text{Wilcoxon}) \), and -1.5 versus -1.1 SD during the second year \( (P = .61) \). Growth rates during the second year correlated with growth rates during the first year \( (r = .36, P = .046) \). Growth rates during the first year were lower in patients who had been given prior cranial irradiation, those who were near pubertal age at the time of transplant, and those who were transplanted for a disease other than acute lymphoblastic leukemia (ALL). During the second year, poor rates of growth were associated only with the use of corticosteroids after transplant.

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and tables of recurrent length percentiles (for ages 0 to 2). An SD score (Z score) was calculated for height as (height minus mean height for sex and age) divided by SD of height for sex and age, and for growth rate as (growth rate minus mean growth rate for age and sex) divided by SD of growth rate for age and sex, using a computer algorithm. A child that was average (ie, at the mean) in height or height for sex and age) divided by SD of height for sex and age, and

Growth hormone levels after glucagon stimulation by chemoluminescent immune-metric assay (TDx; Abbott Laboratories, Dallas, TX). Patients were divided into approximately two equal-sized groups according to date of transplant (before and after 1986 divided the group into halves), to determine if any of the changes in supportive care over time may have unexpectedly had an influence on growth. The number of induction treatment courses used before transplant was considered as a crude index of the cumulative intensity of prior therapy. The use of corticosteroids at any time after transplant was lumped together irrespective of the timing, dose schedule, or length of treatment.

Analysis. All height and growth rate determinations were expressed as Z scores. Analyses comparing height and growth rate Z scores between groups were performed using the nonparametric Wilcoxon rank-sum test. χ² tests and Fisher’s exact tests were used to test the associations between treatment groups and categorical factors. Correlation coefficients were calculated to evaluate associations between growth rate Z scores and continuous factors. The simultaneous effect of two or more factors on 1- and 2-year growth rate z scores was studied using multiple linear regression analysis.

RESULTS

Pretransplant and posttransplant heights. Pretransplant height Z scores were used as a gauge of the influence of prior treatment or other factors on growth independent of the transplant experience. The median pretransplant height was -0.2 SD below normal (range, -2.5 to +3.0); height greater than 2.0 SD below normal was observed in only three patients (6%). The pretransplant heights were comparable in the BU/CY and CY/TBI groups (-0.1 v -0.6 SD, P = .35, Wilcoxon) (Fig 1). Although there was a marginal overall trend that children who had been given prior cranial irradiation were shorter than those not irradiated (-0.8 ± 0.98 v 0.0 ± 1.14, P = .06), within each transplant treatment assignment group, pretransplant heights did not differ with respect to the administration of prior cranial irradiation (P = .11 for CY/TBI and P = .34 for BU/CY). Among those irradiated, there was no association of pretransplant height with the cumulative dose (eg, the median height was -0.95 ± 0.74 SD for those given 18 Gy, v -0.60 ± 0.89 SD for those given 24 Gy).

At 1 and 2 years after transplant, respectively, the median height Z scores were -0.7 (range, -3.0 to +1.3) and -0.9 (range, -4.8 to +1.0) SD below normal. The 1- and 2-year heights were 2 or more SD below normal in seven of 47 (15%) and eight of 31 (26%) patients, respectively. Height Z scores in patients treated with BU/CY were comparable to those treated with CY/TBI: -0.45 v -0.8 SD at 1 year (P = .79), and -0.90 versus -0.95 SD below normal at 2 years (P = .53) (Fig 1).

Growth rates overall and according to preparative regimen. The median growth rates were -2.2 SD (range, -7.1 to +6.1) and -1.4 SD (range, -7.3 to +2.0) below normal during the first and second years, respectively. Growth rates were greater than 2.0 SD below normal in 24 of 47 (51%) children during the first year after transplant. Growth rates were greater than 2.0 SD below normal in 12 of 31 (39%) children during the second year after transplant. Growth rates in patients treated with BU/CY were comparable to those treated with CY/TBI: -2.5 (range, -7.1 to +2.3) versus -1.7 (range, -5.7 to +6.1) SD below normal during the first year (P = .19, Wilcoxon), and -1.5 (range, -5.0 to +2.0) versus -1.1 (range, -7.3 to 1.7) SD below normal during the second year (P = .61) (Fig 2). In children treated with CY/TBI, growth rates were greater than 2.0 SD below normal in 10 of 23 (43%) and five of 16 (31%) during the

![Fig 1. Heights before and at 1 and 2 years after transplant in 47 children grouped according to preparative regimen. Twenty-four children received BU/CY and 23 received CY/TBI. Values are expressed as age- and sex-adjusted SDS (Z scores) from population normals. There were no significant differences in heights between the groups receiving BU/CY and CY/TBI at any of the three time points. (■) Overall.](image)
first and second years, respectively. In children treated by
BU/CY, growth rates were greater than 2.0 SD below
normal in 14 of 23 (61%) and seven of 15 (47%) during
the first and second years, respectively. The median first-year
growth rates of patients with ALL who did or did not
receive cranial irradiation were −2.4 and −0.3 SD, respec-
tively; this compared with first-year growth rates in patients
with other diagnoses with and without cranial irradiation of
−1.8 and −3.0 SD. Thus, the poorer first-year growth in
non-ALL patients even without cranial irradiation (−3.0
SD) compared with patients with ALL given cranial irradia-
tion (−2.4 SD) explains the apparent paradox of ALL
patients having better first-year growth despite the majority
(16/23) having had cranial irradiation.

Growth rates during the second year correlated with
growth during the first year ($r = .36$, $P = .046$). In 43% of
patients, the growth rate during the second year exceeded
that of the first year; conversely, it was lower in 57% of
children with paired observations.

To determine if there was a significant increase in growth
between the first and second years, the difference was taken
between the first- and second-year growth rate Z scores.
The proportion of patients with a positive change was
calculated and tested to determine if this proportion was
significantly different from .5 (which would be expected
by chance). Using a two-sided, one-population hypothesis test
for the proportion, we determined that there was not a
significant increase in growth during the second year
($P = .25$).

Influence of factors other than preparative regimen on
growth. Children nearing pubertal age grew at a slower
rate during the first year after transplant than younger
children ($−5.7 v −1.8$ SD, $P = .03$). The use of corticostero-
doids was also associated with slower growth rates during
the first year ($−2.4 v −1.6$ SD, $P = .05$). Patients who received
transplants for the diagnosis of ALL grew at a greater rate
during the first year than those transplanted for other
diagnoses ($−1.7 v −3.0$ SD, $P = .077$). In the entire group
of patients, prior cranial irradiation was not associated with
the rate of growth during the first year after transplant
($−2.2 v −1.6$ SD, $P = .42$). However, in patients treated
with CY/TBI, prior cranial irradiation was associated with
growth rate impairment during the first year ($−2.6$ SD $v
−0.9$ SD, $P = .025$), but not in patients treated with
BU/CY ($P = .70$) (Fig 3). The occurrence of acute GVHD
($P = .13$), and an older pretransplant age ($P = .06$), were
marginally associated with impaired growth rates during
the first year. Gender ($P = .38$), type of transplant ($P = .99$),
year of transplant ($P = .62$), occurrence of chronic GVHD
($P = .28$), number of prior treatments ($P = .45$), and pre-
transplant height ($P = .50$) were not associated with growth
rates during the first year after transplant.

Multiple linear regression was used to determine which
combination of these factors could best explain the varia-
tion in one-year growth rate Z scores. The potential
interactions between diagnosis, cranial irradiation, and
the number of prior treatment courses were evaluated, but
none influenced the final regression model, except for a
marginally significant interaction between diagnosis and
cranial irradiation ($P = .083$). Therefore, diagnosis, cranial
irradiation, and their interaction were tested along with the
other variables associated with growth rates with $P$ values
less than or equal to .15 in the multivariate model. The
independent factors identified by this multivariate analysis
and the equations for first- and second-year growth rate Z
scores generated by these multivariate models are given in
Table 2.
**Table 2. Association of Various Factors on Growth Rates During the First and Second Years by Multiple Linear Regression Analyses**

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Coefficient</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis other than ALL (n = 24)</td>
<td>-2.22451</td>
<td>0.7672</td>
<td>.0059</td>
</tr>
<tr>
<td>Prior cranial irradiation (n = 21)</td>
<td>-2.04942</td>
<td>0.7814</td>
<td>.0120</td>
</tr>
<tr>
<td>Near pubertal age†</td>
<td>-2.8412</td>
<td>1.1008</td>
<td>.0133</td>
</tr>
<tr>
<td>First-year growth Z score‡ = +0.0857 - 2.22451(DX) - 2.04942(CRT) - 2.8412(PUB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of corticosteroids (n = 19)</td>
<td>-1.72807</td>
<td>0.7928</td>
<td>.0376</td>
</tr>
<tr>
<td>Second-year growth Z score‡ = -0.6666 - 1.72807(STER)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Factors were dichotomized as follows: ALL or other disease (DX), 0 = ALL, 1 = other; cranial irradiation (CRT), 0 = no, 1 = yes; near pubertal age (PUB), 0 = no, 1 = yes; corticosteroids (STER), 0 = no, 1 = yes.

†Boys were considered near pubertal age if age > 11.0, and girls if age > 9.0.

‡The regression equations for the Z scores of the growth rates during the first and second years after transplant.

**DISCUSSION**

Growth impairment has been a common observation in children treated for hematologic malignancies. This has been most consistently found in children who received cranial irradiation. Both larger dose fractions[^1] and higher total doses[^2] of radiotherapy have been implicated as major determinants of the frequency and degree of persistent growth impairment. The age of the patient at the time of treatment has also been implicated.[^3] Moreover, some evidence suggests that the underlying disease itself (viz, ALL) may suppress growth, and growth may resume after effective control of the malignancy.[^4] There are conflicting data as to whether intensive chemotherapy regimens in the absence of cranial radiotherapy are regularly associated with persistent growth impairment; some reports have found persistent impairment not adequately explained by cranial radiotherapy,[^5] while others have not.[^6] However, animal models and anecdotal reports have shown diminished bone formation and reduced osteoblast function by several chemotherapeutic agents.[^7] Gender has been implicated as a determinant, with girls being more sensitive to the effects of radiotherapy.[^8] Corticosteroids, which are often used during the course of these various regimens, have been associated with growth impairment.

Growth in children treated by BMT using TBI has been similarly found to be retarded.[^9] In contrast, growth after BMT using CY alone was not adversely affected.[^10] To our knowledge, only one preliminary report has presented data in children using a regimen containing BU/CY.[^11] Manenti et al.[^12] examined the growth velocity in children transplanted for thalassemia major. The BU/CY regimen was similar to that used in this report, although the dose of busulfan was lower (14 mg/kg compared with 16 mg/kg in this report). Growth velocity was not impaired in younger children (age, < 9), but was impaired in older children (age, 10 to 15). There was no breakdown as to first- or second-year growth rates for comparison with this report. There were no growth hormone or somatomedin assessments in the patients. The explanation for the minor effect of BU on growth in younger children in that report may be the decreased bioavailability of BU noted in children aged 5 or younger.[^13] Alternatively, the administration of prior chemotherapy, such as given to the patients in this study (but not given to thalassemia patients), may have influenced the effect of the transplant preparative therapy on host tissues.

The data in this study indicate a striking effect on the growth rates of many children treated by BU/CY, an effect comparable to that of CY/TBI. In contrast to Manenti et al, we did see impaired growth rates in younger children, perhaps because of the higher dose used in these patients. Age did not affect growth rates in this series, but growth rates in children nearing pubertal age were especially retarded, presumably because of failure or delay of spontaneous pubertal development, and because the growth rates of normal children increase at pubertal age. Moreover, growth rates in children transplanted for ALL were less impaired than growth rates in children transplanted for other diseases (independent of the transplant preparative...
regimen). There was no evidence of a compensatory growth spurt during the second year, using paired measurements. While cranial radiotherapy further compromised the growth rates of children given TBI during the first year, it did not affect the growth rates of children treated by BU/CY, and the effect of cranial irradiation on growth was not evident during the second year. The growth impairment in these children appears to be attributable to the transplant preparative regimen, rather than events before the transplant, since the height at the time of transplant was comparable to the age- and sex-adjusted means.

Growth hormone deficiency has been implicated as a cause of growth impairment in many children treated for malignancy, especially when cranial irradiation has been used through either hypothalamic or pituitary dysfunction. In some studies, growth proceeded at a normal rate despite blunt growth hormone responses to provocation. Moreover, some studies have shown poor correlation of growth hormone responses with growth rates. Other studies suggest mechanisms other than growth hormone deficiency.

In two earlier reports in children treated by TBI as part of the BMT preparative regimen, evidence of impaired GH responses was noted. Sanders et al reported that two thirds of children with prior cranial irradiation (but none without cranial irradiation) and 10 of 18 children given unfractionated TBI had impaired growth hormone secretion after a provocative test; subnormal growth hormone responses were noted in an additional four of 25 patients with and 10 of 26 without cranial radiotherapy. Similarly, in Borgstrom’s series, 21 children transplanted using unfractionated TBI of 10 Gy grew poorly and 10 of 18 had subnormal growth hormone responses after provocative testing, while three children transplanted with CY alone grew normally. In Borgstrom’s study, abnormal growth hormone provocative test findings increased over time: only 10% of children had low responses in the first year after BMT, but after 3 years, subnormal responses were seen in 56%. Five of seven children treated with growth hormone responded. The mechanism of growth retardation of the patients in this series is less clear. Of the seven patients with growth rates greater than 2 SD below normal for age tested with a provocative test for growth hormone stimulation, all had normal growth hormone responses. This suggests that impaired growth hormone secretion may not be the explanation, at least for most of these children during these early years after transplant. However, patients with a normal growth hormone response to insulin-induced hypoglycemia have been shown to have diminished spontaneous pulsatile secretion, suggesting that the latter measurement may be a more sensitive indicator of quantitative growth hormone abnormalities, although this method is controversial. The fact that somatomedin levels were below the mean for age and sex in 14 of 21 children tested suggest that a subtle growth hormone deficiency may become present. With longer follow-up, the growth hormone deficiency may become more prominent. The absence of elevated somatomedin levels argue against an altered sensitivity of local tissue receptors to growth factors as a prominent factor in the growth retardation. One report in children with ALL, in which somatomedin levels dropped and growth improved after treatment of the ALL, suggests impaired tissue responsiveness to growth factors may occur in some patients as a cause of growth disturbance. There was no evidence of malnutrition or other endocrine disturbances that may have affected growth in these children.

In conclusion, growth rate impairment was common in these patients undergoing BMT. The adverse affect appeared to be due to transplant events, since pretransplant heights were similar to age- and sex-adjusted norms. The effect of BU/CY was comparable to that of CY/TBI (using a fractionated regimen). Growth rates after the first year after transplant were affected by prior cranial irradiation, diagnosis, and near pubertal age, while growth rates during the second year were affected only by use of corticosteroid use. The influence of pretransplant events (such as prior cranial irradiation) on the growth after transplant suggests an interaction of these events with the transplant preparative therapy to potentiate growth retardation. Further study will be needed to ascertain whether there is any catch-up growth with longer follow-up and whether subtle growth hormone deficiency may become manifest. More information is needed as to how much growth will occur once puberty does take place.

REFERENCES
8. Wingard JR, Piantadosi S, Santos GW, Saral R, Vriesendorp HM, Yeager AM, Burns WH, Ambinder RF, Braine HG, Elfen-


Growth in children after bone marrow transplantation: busulfan plus cyclophosphamide versus cyclophosphamide plus total body irradiation

JR Wingard, LP Plotnick, CS Freemer, M Zahurak, S Piantadosi, DF Miller, HM Vriesendorp, AM Yeager and GW Santos