Growth in Children After Bone Marrow Transplantation: Busulfan Plus Cyclophosphamide Versus Cyclophosphamide Plus Total Body Irradiation

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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 weight 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 (-0.1 v -0.6 SD, \(P = .35\)). 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.

GROWTH RETARDATION has been a frequent accompaniment of cancer treatment in children. Previous studies have shown that children who underwent bone marrow transplantation (BMT) using cyclophosphamide plus fractionated total body irradiation (CY/TBI) experienced growth impairment. In those studies, prior cranial irradiation, single-dose TBI, and chronic graft-versus-host disease (GVHD) treated with corticosteroids significantly influenced growth. Growth hormone deficiency was implicated as the cause in some of the patients, but other factors possibly adversely influencing growth were also suggested.

Busulfan plus cyclophosphamide (BU/CY) has gained increasing use, especially in nonlymphocytic leukemias, lymphomas, and thalassemia, as an alternative to TBI-containing preparative transplant regimens. There has been considerable interest in ascertaining whether growth and other late toxicities would be less affected, since chemotherapy regimens used in the treatment of acute lymphoblastic leukemia (ALL) without irradiation have been associated with less growth suppression. In this study, we report the yearly growth rates of 24 children given the BU/CY preparative regimen, compare them with those of 23 children given CY/TBI, and examine a variety of factors that influenced the rates of growth. We find that growth in children transplanted for ALL was less impaired than in children transplanted for other diseases, that somatomedin levels and growth hormone responses to stimulation were not associated with growth during the first 2 years after transplant, and that growth in children administered BU/CY was no better than in children treated by CY/TBI.

MATERIALS AND METHODS

Patients. Records were reviewed of 72 children who received autologous, allogeneic, or syngeneic BMTs at the Johns Hopkins Oncology Center with CY/TBI or BU/CY between July 1977 and July 1989, who were under the age of 12 at the time of transplant, and who had a disease-free survival of at least 180 days. Of these 72 children, 47 had both pretransplant and posttransplant height measurements. Forty-seven had determinations at 1 year and 31 had determinations at 2 years. Descriptive features of these children are provided in Table 1. Prior irradiation to either head (16), spine (one), or both (five) had been given to 33% of children treated by BU/CY and 61% of those treated by CY/TBI. Cumulative fractionated doses to the cranium were as follows: six children had received 18 Gy, one 19.8 Gy, one 20 Gy, nine 24 Gy, one 44 Gy, and three had no details of their prior cranial radiotherapy. Cumulative irradiation doses to the spine were as follows: 4.4, 10, 12, 20, 30.4, and 50 Gy. Because of treatment assignment, 87% of patients given CY/TBI were transplanted for ALL, while only 22% of patients treated with BU/CY had this diagnosis. Patients were classed as nearing pubertal age if age was greater than 11.0 years for boys or greater than 9.0 years for girls. Four of the five children near pubertal age were girls (age, 9.6, 11.2, 11.5, and 11.8 years) and the fifth, a boy, was aged 11.9 years. The diagnoses were ALL (23), acute myelogenous leukemia (16), lymphoma (three), and others (five).

Preparative regimens, marrow transplantation procedures, and growth assessments. Patients received BU/CY in preparation for transplantation at doses of BU 1 mg/kg every 6 hours for 4 days (16 mg/kg total) followed by CY 50 mg/kg (based on ideal weight) daily for 4 days as previously published or CY 50 mg/kg/d for 4 days plus fractionated TBI given as 3 Gy/d for 4 days with lung shielding on the third day as previously described. Transplant supportive care was performed according to previously described procedures.

Height determinations were performed using a stadiometer before and after transplant at approximately 12 and 24 months. The height and growth rates were compared with means ± SD of height and growth rates for age and sex using the National Center for Health Statistics Tables of Stature percentiles (for ages 2 to 18).
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 sex and age, using a computer algorithm. A child that was average (ie, at the mean) in height or growth rate, thus had a Z score equal to 0. Bone age was assessed at 1 year from radiographs of the hand and wrist using the method of Greulich and Pyle. Growth hormone levels after glucagon stimulation were measured at 1 year as previously described. At 1 year, 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 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) 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%) 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
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, respectively; 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 irradiation (−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 −1.65 SD, P = .02). 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 pretransplant 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 variation 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.
GROWTH IMPAIRMENT IN YOUNG children has been reported after bone marrow transplantation (BMT) for hematologic malignancies. This study assessed growth in children transplanted for ALL, comparing those treated by busulfan/cyclophosphamide (BU/CY) with those treated by cyclosporine/total body irradiation (CY/TBI).

**Materials and Methods:**
A prospective study included 72 children with ALL transplanted between 1982 and 1986. Growth was evaluated at the time of diagnosis and at two, four, and six years after BMT. Growth parameters included height, weight, and pubertal status.

**Results:**
Growth impairment was observed in 35% of patients, with 22% of patients growing below the mean for age and sex, and 3% growing below the mean for age and sex-adjusted mean (Z score). The use of corticosteroids after transplant was the only factor significantly associated with impaired growth rates during the first and second years after transplant. Boys were considered near pubertal age if age > 10.0, 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 were:

**First year**
- Diagnosis other than ALL (n = 24): \(-2.22451 \quad 0.7672 \quad .0059\)
- Prior cranial irradiation (n = 21): \(-2.04942 \quad 0.7814 \quad .0120\)
- Near pubertal age (n = 5): \(-2.84120 \quad 1.1006 \quad .0133\)

**Second year**
- Use of corticosteroids (n = 19): \(-1.72807 \quad 0.7928 \quad .0376\)
- Second-year growth Z score: \(0.6666 - 1.72807[\text{STER}]\)

**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 and higher total doses 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. Moreover, some evidence suggests that the underlying disease itself (viz, ALL) may suppress growth, and growth may resume after effective control of the malignancy. 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, while others have not.

The use of corticosteroids after transplant was the only factor significantly associated with impaired growth rates during the second year after transplant. Growth hormone and somatomedin levels were also evaluated. Somatomedin levels were assayed in 21 children. Levels were normal for age and sex in 18, low in three, and high in none. On average, the somatomedin levels were 0.82 times the age- and sex-adjusted mean (range, 0.25 to 2.8 times the mean). There was no significant correlation between the somatomedin levels and growth rates. 13 of the 24 children with growth rate Z scores greater than 2.0 SD below normal had somatomedin levels assayed: 10 were in the normal range for age and sex (6 of the 10 were below the mean for age and sex) and three were low. Six of 11 patients treated by BU/CY had somatomedin levels below the mean for age and sex, while eight of 10 patients treated by CY/TBI had levels below the mean.

**Other Endocrine Evaluations:** Serum thyroxine levels were normal in all patients tested (36%); although TSH levels were elevated in five of 17 (29%) patients tested (range, 5.7 to 9.0, with normal < 5.0 mU/mL), all had normal thyroxine levels. Plasma cortisol levels at 8:00 AM were normal in all patients tested (43%). No patient was significantly malnourished (actual weight not > 5% below ideal body weight). Bone age 1 to 2 years after BMT was normal for chronologic age in all patients tested (30%).

**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>
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<tbody>
<tr>
<td>Diagnosis other than ALL (n = 24)</td>
<td>-2.22451</td>
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<td>1.1006</td>
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</tr>
<tr>
<td>First-year growth Z score (DX)</td>
<td>+0.00857 - 2.22451[DX] = -2.04942[CRT] - 2.84120[PUB]</td>
<td></td>
<td></td>
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<tr>
<td>Second-year growth Z score</td>
<td>-0.6666 - 1.72807[STER]</td>
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*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.

**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 and higher total doses 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. Moreover, some evidence suggests that the underlying disease itself (viz, ALL) may suppress growth, and growth may resume after effective control of the malignancy. 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, while others have not. However, animal models and anecdotal reports have shown diminished bone formation and reduced osteoblast function by several chemotherapeutic agents. Gender has been implicated as a determinant, with girls being more sensitive to the effects of radiotherapy. 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 CY alone was not adversely affected. In contrast, growth after BMT using CY alone was not adversely affected. To our knowledge, only one preliminary report has presented data in children using a regimen containing BU/CY. Manenti et al 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. 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 blunted 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 be 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 effect 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 during 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.

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bein G, Jones RJ, Kaizer H, May WS, Rowley SD, Sensenbrenner LL, Stuart GROWTH IN CHILDREN AFTER MARROW TRANSPLANT 1073


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