Pubertal Growth in Young Adult Survivors of Childhood Leukemia

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Purpose: To determine the effect of cranial irradiation (18 Gy and 24 Gy) on pubertal growth in young adult survivors of childhood acute lymphoblastic leukemia (ALL).

Patients and Methods: Final height (FH) and pubertal growth were retrospectively examined in 142 young adult survivors of childhood ALL. All were in first remission and had received either 18 or 24 Gy of cranial irradiation. Eighty-four children (48 girls) were treated with 24 Gy and 58 (35 girls) with 18 Gy. None had received either testicular or spinal irradiation. Timing and duration of puberty were studied in 110 patients.

Results: Significant reduction in height standard deviation score (SDS) from diagnosis to FH was seen in both sexes and in both dose groups. In girls, in both dose groups, mean age at peak height velocity (PHV) and mean age at menarche occurred significantly earlier than in the normal population. In boys, there was a normal timing of PHV. The amplitude of PHV was significantly reduced in both sexes and in both dose groups. Parameters of pubertal duration (PHV to menarche, PHV to FH, and menarche to FH) were not significantly different from normal population values.

Conclusion: In conclusion, puberty occurred early in girls, but not in boys. Amplitude of PHV was reduced in both sexes, with no reduction in the duration of puberty. It is likely that disturbances of both timing and quality of growth during puberty contribute to the loss of standing height and body disproportion seen in these children.

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ACUTE LYMPHOBLASTIC leukemia (ALL) is the most common childhood malignancy, with an incidence of 3.5 per 100,000. Survival rates for children with ALL have improved enormously over the last 20 years, such that 70% of children can now expect to be long-term survivors with current therapy.[1,2] Since 1970, this has in part been achieved by the introduction of treatment directed at the CNS, with a combination of cranial irradiation and intrathecal methotrexate.[3] Until 1980, the dose of cranial irradiation given was 24 Gy (usually administered in 15 fractions over 3 weeks). This was reduced to 18 Gy (administered in 10 fractions over 2 weeks) in 1981 in an attempt to reduce the morbidity seen with the higher dose.

It is well recognized that higher doses of cranial irradiation (21 to 24 Gy) can cause significant loss in standing height.[4-6] At lower doses, the effects on growth and, more importantly, on final height have been less clear.[6-8] Early and precocious puberty in girls have also been reported after both doses of cranial irradiation.[6,9]

Disproportion at final height after treatment for ALL in childhood was recently reported by our group. This suggests that at least in some children, much if not all of the height loss is due to a reduction in sitting height.[10]

In this study, we examined the effect of both 18 Gy and 24 Gy of cranial irradiation on growth and the timing and duration of puberty.

PATIENTS AND METHODS

Young adult survivors of childhood ALL were identified from three regional pediatric oncology/hematology centers. All had received combination chemotherapy and cranial irradiation as CNS prophylaxis. All were in first remission, and none had received either spinal or gonadal irradiation. All had achieved final height. Children who had received growth hormone (n = 15) or sex corticosteroids (n = 3) were excluded (all 18 had received 24 Gy). Details of chemotherapy and radiotherapy were obtained from clinical records.

The children were divided into four groups by sex and dose of radiotherapy received. The group 24G consisted of girls who had received 21 to 24 Gy, and the group 24B of boys who had received 21 to 24 Gy. The groups 18G and 18B consisted of girls and boys, respectively, who received 18 Gy of cranial irradiation. Each group was then further divided by age at diagnosis (< or > 7 years). The age of 7 years was arbitrarily chosen to provide a group of children treated prepubertally in whom the pubertal growth pattern could be evaluated, independent of any catch-up growth phenomenon. In addition, this is the dividing age used by previous investigators[6,11] and allowed comparison of our data with theirs.

Standard chemotherapy regimens were used for all patients (eg, United Kingdom Acute Lymphoblastic Leukaemia [UKALL] trials I, II, III, V, VII, and VIII). These consisted of induction of remission using three or four drugs (eg, asparaginase, vincristine, and prednisolone, plus one or two additional agents in UKALL X). This was followed by a period of intensification in some, and then by a four-drug maintainance regimen (oral methotrexate, mercaptopurine, vincristine, and prednisolone). A subgroup (n = 8) received more toxic chemotherapy (UKALL IV and VI and Memphis V), in that they

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received intravenous cyclophosphamide during both induction and maintainance chemotherapy. This subgroup of patients were all in the 24-Gy group. No patient received intravenous methotrexate.

All available auxologic data on each child were examined. All had been measured serially from diagnosis using a standing height stadiometer. The majority of measurements were made every 6 to 12 months, with a few (n = 5) being a maximum of 15 months apart. Final height (FH) was defined as height reached when the height velocity over the preceding year was less than 1 cm/yr. Standing height standard deviation score (SDS) at diagnosis and at FH were calculated using the standards reported by Tanner et al.[12] Change in SDS was the difference in SDS between diagnosis and FH.

Timing of puberty and growth during puberty were studied using age at peak height velocity (PHV; mid age over which maximal growth velocity occurred), amplitude of PHV (pubertal growth spurt), age at menarche in girls, and age at FH. The completeness and reliability of data related to age at onset of puberty were deemed inadequate for inclusion in the study.

Parameters of duration of pubertal growth were calculated by subtracting age at PHV from age at menarche, age at menarche from age at FH, and age at PHV from age at FH. For those girls in whom height at menarche was available (included if there was a measurement within 2 months of the date of menarche), residual growth from menarche to FH was calculated. Comparison with contemporary British normal population data was made for the parameters of pubertal growth.[13]

A subset of girls with early puberty (age at PHV < 10.9 years) was identified from both dose groups. This subdivision was chosen to allow comparison with the normal early developers identified from the cohort of Leeds children studied by Buckler.[13]

Statistics

Paired *t* tests were used to compare height SDS at diagnosis with height SDS at FH. Unpaired *t* tests were used to compare the parameters of pubertal growth between groups, and then with normal population data.

RESULTS

Patients

One hundred forty-two children were eligible for inclusion in the study. Of these 84 (60%) had received 21 to 24 Gy (48 girls and 36 boys; cranial dose 21 Gy, n = 9) and 58 (40%) had received 18 Gy (35 girls and 23 boys).

For analysis of timing and duration of puberty, girls older than 11 years and boys older than 13 years at diagnosis were excluded (11 of 142). A further 21 children were excluded due to incomplete pubertal data. Age at diagnosis, age at final evaluation (FH), and length of time off therapy are listed for each of the four groups in Table 1.

Table 1. ALL Groups: Age at Diagnosis, Age at Final Evaluation, and Length of Time Off Treatment

	Age at Diagnosis (yr)		Age at Final Evaluation (yr)*	Time Off Therapy (yr)	
Group	Median	Range	Mean ± SD	Median	Range
18 Gy girls	6.2	2.4-10.7	14.8 ± 1.0	7.2	3.3-10
18 Gy boys	8.3	1.7-12.5	17.2 ± 0.8	6.7	3.0-13.9
24 Gy girls	4.1	1.4-10.5	15.2 ± 0.8	9.3	5.6-12.0
24 Gy boys	4.8	1.6-11.2	17.9 ± 1.1	10.8	5.1-15.2

Abbreviation: yr, years.

*At adult height (ie, when growth is < 1 cm/yr in the preceding year).

Effect on FH

FH data are reported in detail elsewhere,[10] but are included here in brief to aid description of the study population. Significant reduction in final height SDS was seen in both dose groups and in both sexes. Mean changes in height SDS from diagnosis to final height for the 24G and 24B groups were −1.55 and −0.9, respectively, and for the 18G and 18B groups, −1.1 and −0.7, respectively. In terms of actual centimeters lost, 23 (48%) of the 24G group, 11 (31%) of the 24B group, 10 (29%) of the 18G group, and four (17%) of the 18B group had a change in height SDS equivalent to a loss in height of ≥10 cm.

Effect on Timing of Puberty

Mean age at PHV and age at menarche are listed in Tables 2 and 3. In girls in both dose groups, PHV occurred significantly earlier than in the normal population (12.1 years) at a mean of 10.7 ($P < .001$) and 11.0 ($P < .001$) years, respectively, for the 24G and 18G groups. Age at menarche was also significantly earlier than the normal population mean (13.4 years) in both dose groups at a mean of 12.2 ($P < .001$) and 12.3 ($P < .001$) years, respectively, for the 24G and 18G groups. Further analysis by age at diagnosis demonstrated that it was only in those patients who were younger at diagnosis (< 7 years) in both dose groups that this difference was significant ($P = .001$ and $P = .0001$, respectively). In boys, in both dose groups, age at PHV was not significantly different from normal population data (Table 3).

Effect on PHV

PHV in all four groups is listed in Tables 2 and 3. In girls, the magnitude of PHV was not significantly different from normal population values for girls with normal timing of puberty. However, PHV and age at PHV are not independent variables, with earlier onset of PHV associated in normal children with a greater magnitude of pubertal growth spurt (see later).

In younger girls (< 7 years), there was a reduction in PHV when compared with girls older than 7 years at diagnosis; this difference was statistically significant only in the 24Gy group ($P = .03$).

In boys, in both dose groups, PHV was significantly

Table 2. Girls: Age at PHV, Age at Menarche, and Magnitude of PHV in 18-Gy and 24-Gy Groups, With Comparable Normal Data

Girls	Age at PHV (yr)			Age at Menarche (yr)			PHV (cm/yr)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
18 Gy									
Total group	22	11.0*	1.16	26	12.3*	1.3	22	8.1	1.07
< 7 years at diagnosis	14	10.4†	0.7	15	11.7†	0.74	14	7.9	1.07
> 7 years at diagnosis	8	12.1	0.7	11	13.1	0.78	8	8.9	1.4
24 Gy									
Total group	42	10.7*	1.06	39	12.2*	0.8	42	7.8	1.2
< 7 years at diagnosis	36	10.5	0.9	34	12.1†	0.9	36	7.4†	1.15
> 7 years at diagnosis	6	11.6	1.2	5	12.7	0.3	6	8.8	1.1
Normal population	102	12.1	0.98	102	13.4	1.1	102	8.1	1.07

*Group mean significantly different from population mean.
†Mean of group < 7 years at diagnosis significantly different from mean of group > 7 years at diagnosis.

less than normal population values ($P < .001$ and $P < .05$, for 24B and 18B, respectively).

Effect on Duration of Puberty

The mean interval from age at PHV to age at FH was not significantly reduced in either girls (Table 4) or boys. Indeed, in the 24G and 24B groups, it appeared to be significantly longer than normal population values ($P < .001$ and $P < .01$, respectively). Age at PHV to age at menarche, and age at menarche to age at FH, are also listed in Table 4.

Growth in Early-Developing Girls

Table 5 lists data for girls in both dose groups whose age at PHV was less than 10.9 years compared with normal data.[13] Mean PHV was significantly reduced at 7.7 and 7.9 cm/yr for the 24G ($P < .001$) and 18G ($P < .01$) groups when compared with the normal early-developing girls (9.01 cm/yr). Girls in both dose groups also had significantly less growth after menarche (mean, 5.8 cm 6.2 cm, respectively, for 24G [$P < .01$] and 18G [$P < .02$] groups, compared with 8.6 cm in the normal population).

In the 24G group, PHV to menarche was significantly longer than in the normal group ($P < .001$), with the time from menarche to FH being significantly shorter ($P < .01$). PHV to FH was not significantly different between the groups.

Table 3. Boys: Age at PHV and Magnitude of PHV in 18-Gy and 24-Gy Groups, With Comparable Normal Data

Boys	Age at PHV (yr)			PHV (cm/yr)		
	n	Mean	SD	n	Mean	SD
18 Gy						
Total group	16	14.0	1.0	16	9.2*	1.0
< 7 years at diagnosis	6	14.1	1.1	6	8.8	1.55
> 7 years at diagnosis	10	13.8	0.8	10	9.5	2.04
24 Gy						
Total group	30	13.9	1.0	30	8.7*	1.5
< 7 years at diagnosis	23	13.8	1.1	23	8.4	1.16
> 7 years at diagnosis	7	14.1	0.8	7	9.5	1.77
Normal population	216	14.1	1.0	216	9.8	1.2

*Group mean significantly different from population mean.

DISCUSSION

Data on growth and pubertal disturbance following treatment for childhood ALL are conflicting.[4-7] Treatment variables, particularly differences in chemotherapy schedules and variation in total dose and fractionation of cranial irradiation, may account for some of the discrepancies. In addition, it is only recently that sufficient long-term survivors have reached adulthood to allow the final impact on growth and adult stature to be assessed.[5,6,8,11]

We have previously reported a loss in standing height at FH after both 18 Gy and 24 Gy of cranial irradiation that is of a similar magnitude to that reported by previous investigators.[6,8,10,14] Much of this height loss is due to body disproportion, ie, a loss in sitting height.[10] In this study, we have examined pubertal growth in an attempt to explain this disproportion, as much of normal spinal growth occurs during puberty.

We have shown that in girls less than 7 years of age at diagnosis, both PHV and menarche occur significantly earlier than normal. Early onset of puberty was also observed in girls less than 7 years of age at diagnosis by Ureuna et al,[6] with earlier onset of puberty correlating with the lower dosage of irradiation. In contrast, other investigators have found normal timing of puberty in their study groups.[11,15] Both of the latter studies include only small numbers at FH.

In boys, we report normal timing of PHV. We do not have sufficient data to comment on the onset of puberty

Table 4. Girls: Interval Between Stages of Puberty, and Magnitude of Height Increment From Menarche to FH, With Comparable Normal Data

Girls	Age at PHV to Age at Menarche (yr)			Age at Menarche to Age at FH (yr)			Age at PHV to Age at FH (yr)			Menarche to FH (cm)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
18 Gy												
Total group	19	1.3	0.76	19	2.65	0.82	19	3.95	1.18	18	6.03	2.3
< 7 years at diagnosis	12	1.55	0.72	12	2.9	0.72	13	4.18	1.18	9	7.1	1.7
> 7 years at diagnosis	7	0.88	0.66	8	2.2	0.9	6	3.47	1.13	9	4.9	2.4
24 Gy												
Total group	35	1.65*	1.0	35	2.98	0.95	41	4.56*	1.04	24	6.46	3.7
< 7 years at diagnosis	30	1.73	1.03	30	3.04	1.0	35	4.68	0.96	20	6.45	3.9
> 7 years at diagnosis	5	1.16	1.11	5	2.6	0.42	6	3.9	1.33	4	6.5	2.3
Normal population	98	1.23	0.56	76	2.71	1.18	77	3.97	1.03	78	6.1	2.6

*Group mean significantly different from population mean.

in our group, but suspect that there is normal harmony in the sequence of the acquisition of secondary sexual characteristics and the relation of these to the growth spurt, as in a similar cohort of irradiated boys.[9] A trend toward earlier onset of puberty in boys was reported by Ureuna et al,[6] but this was not significantly different from normal population data. Hokken-Koelega et al[11] used life-tables to analyze pubertal onset in boys, and found this to be similar to nonirradiated children.

Other investigators have shown the magnitude of the growth spurt in girls who have received both 18 and 24 Gy to be significantly less than in nonirradiated girls.[9,14-16] In our study, we have shown that the group as a whole did not show a reduction in PHV, but that there was no compensatory increase in PHV in the early-developing girls as occurs in nonirradiated early developers. The greatest reduction also occurs in those who were younger at irradiation.

Few data are available in boys. Hokken-Koelega et al[11] reported a reduction in PHV in irradiated boys, although only four subjects in this study had reached FH. Ureuna et al[6] also reported a reduction in height SDS in both 18- and 24-Gy groups during puberty, although they did not comment on PHV. In our series, PHV was reduced in boys in both dose groups, with a trend to a greater reduction in boys who were younger at diagnosis. As in previous studies, the number of boys older than 7 years at diagnosis who received 18 Gy is small. Also, catch-up growth after completion of treatment may have interfered with assessment of PHV in those who were older at diagnosis, in both sexes.

Duration of puberty has not been studied thoroughly in adult survivors of childhood leukemia, although a reduction in the length of pubertal growth might be expected to contribute to the body disproportion seen in these patients. Quigley et al[17] have shown a reduction in the interval between thelarche and menarche of approximately 1 year in a small number of girls (n = 8) treated with 24 Gy. We have shown no such reduction, but clearly these results must be interpreted with caution, as they do not include complete data on pubertal duration. Also, the comparative normal data set used in this study may include a proportion of children who were not strictly at FH, ie, with continued late adolescent growth.[13] This may explain the apparently longer duration of PHV to FH seen in both girls and boys who had received 24 Gy.

Considerable controversy exists over the biologic contribution of radiation-induced growth hormone deficiency to growth, particularly during puberty. Reduced spontaneous growth hormone secretion during 24-hour profiles has been described in both prepubertal and pubertal girls following 24 Gy of cranial irradiation, with a failure of

Table 5. Girls: Early Developers (age at PHV < 10.9 years)—18-Gy and 24-Gy Groups, With Comparable Normal Data

Girls	PHV to Menarche (yr)			Menarche to FH (yr)			PHV to FH (yrs)			Menarche to FH (cm)			PHV (cm/yr)			Age at Menarche (yr)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
18 Gy*	12	1.5	0.7	14	2.7†	0.9	11	4.4	1.2	11	6.2†	2.6	11	7.9†	1.1	12	11.7	0.8
24 Gy*	23	2.1†	1.0	24	3.1†	0.9	27	5.0	0.9	14	5.8†	3.1	27	7.7†	1.1	23	12.1	0.7
Normal population	20	1.1	0.5	15	3.7	1.1	15	4.7	1.1	16	8.6	2.3	20	9.0	0.6	20	12.0	0.5

*All ages at diagnosis.

†Group mean significantly different from population mean.

the expected increase in growth hormone production at puberty, associated with an attenuated growth spurt.[18] After 18 Gy, physiologic growth hormone secretion was shown to be normal in prepuberty, with an abnormality of periodicity and quantitative reduction in growth hormone secretion seen only during puberty.[19] Chemotherapy also appears to be a factor in growth disturbance[4,8,20] and almost certainly contributes to reduction in FH.

In conclusion, we have shown impairment of pubertal growth in both sexes, with early onset of puberty in girls. The growth impairment may in part be accounted for by abnormalities of growth hormone production, although this does not explain the body disproportion seen in these patients. In addition, the disproportion cannot be explained by a reduction in duration of puberty, although this requires further study. A direct effect of chemotherapy on the spinal epiphyses may contribute.

The etiology of standing height loss after treatment for childhood leukemia is complex and multifactorial. Our study supports the suggestion that those most likely to be affected are girls who are youngest at diagnosis.

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