Growth in Children Treated for Acute Lymphoblastic Leukemia: Single Institution Report from North India

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Abstract Survivors of childhood leukemia are at risk of impaired growth and short stature as adults due to intensive combination chemotherapy and radiation injury. This study was undertaken to evaluate anthropometry in children treated for acute lymphoblastic leukemia (ALL). Children treated for ALL and off treatment for a minimum period of 2 years were evaluated for height, weight and BMI. Z scores were calculated for height, weight and BMI: at induction, 6 months after starting treatment, at end of treatment and at 2 years after completion of therapy. Change in z scores were calculated and compared with CDC criteria and Agarwal standards for Indian children. Fifty two boys and 21 girls were analyzed. Height and weight z scores were seen to show a steep decrease during the initial intensive phase of therapy. The gain in height and weight continued to be slow during therapy and catch up occurred after cessation of therapy. On completion of therapy, patients were shorter, but not significantly so. Girls <9 years were significantly shorter. Weight remained on the lower side of normal. Change of z scores was statistically significant for weight at end of treatment ($p = 0.032$) and 2 years after completion of treatment ($p = 0.00$). BMI z score increased throughout the study period. Peak growth velocities were also late in the study subjects Anthropometric variables of height, weight and BMI are affected by ALL during therapy. Growth deceleration is maximum

during the intensive phase of therapy. Catch up growth occurs but children remain smaller than their peers.

Keywords Acute lymphoblastic leukemia · Height · Weight · Growth velocity · BMI

Introduction

Survival of childhood acute lymphoblastic leukemia (ALL) is now approaching 90 %.The management of ALL is entering a new era with the focus being on ameliorating long term effects of therapy.

Approximately 2/3rd of cancer survivors develop some type of late side effects [1]. Survivors of childhood leukemias are at risk of impaired growth and short stature as adults due to intensive combination chemotherapy and radiation injury to the spine and long bones [2]. The basis of impaired growth in children with ALL includes the disease itself, infections, under nutrition, adverse effects of therapy and cranial radiation (CRT) [2].

It is important to determine whether clinically meaningful growth retardation occurs in these children and whether this adverse outcome is predictable and potentially reversible. Data available on growth and final height in children treated for ALL is conflicting [3–6]. All reports are from developed countries and no literature is available for growth from the developing nations. We studied the pattern of height and weight in children who have completed therapy for ALL.

Patients and Methods

Children who had been treated for ALL at our Institute in the Pediatric Oncology Clinic were the study subjects.

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Inclusion criteria

1. Children in first remission who had completed therapy for ALL and been off treatment for at least 2 years.

Exclusion criteria

1. Children who were less than 2 years or more than 12 years old at the time of diagnosis.
2. Presence of CNS disease at the time of diagnosis.
3. Patients who relapsed/treated for relapse.

All children had received treatment as per the UKALL X protocol. This protocol had CRT (18 Gray units) as central nervous system prophylaxis therapy. Children received three doses of Intra thecal methotrexate during induction and three doses during the central nervous system prophylaxis phase when they received radiation.

Methodology

This was a mixed longitudinal growth data analysis. Data was obtained from the oncology clinic files of patients. The weight and height of the child at the time of diagnosis of ALL was recorded. Subsequently weight and height was chronicled at 6 monthly intervals till the last follow up or a maximum till 18 years of age.

Parameters were plotted on growth charts recommended for Indian children and on the CDC growth charts. SDS scores (z scores) were calculated for height, weight and BMI: at induction, 6 months after starting treatment, at end of treatment and at 2 years after completion of therapy. Change in z scores was then calculated and plotted on graphs. Institutional ethics committee approval was taken for this study.

Statistical Analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 13.0 for Windows). All quantitative variables were estimated using mean, median & standard deviation (SD). Velocity growth (rate of growth) related statistics were also calculated in terms of mean and SD for every anthropometric parameter. SDS scores were calculated by comparing observations with mean and SD in normal population of comparable age and sex. Normality of data was checked by measures of Kolmogorov–Smirnov tests of normality. For normally distributed data means were compared using student's *t* test for two groups and one-way ANOVA (analysis of variance) was used for more than two groups. For skewed data Mann–Whitney test was applied for two groups and for more than two groups Kruskal–Wallis test was applied. To assess the quantum of catch-up

growth experienced by children z-scores were calculated. All statistical tests were two-sided and performed at a significance level of $\alpha = 0.05$.

Results

52 boys and 21 girls were analyzed for growth. The mean age at diagnosis was 5.0 years (2–12 years). At the time of study the median age was 10.25 years (5.5–17 years). A total of 816 observations of height and weight were made. Mean and SD of the height and weight of subjects was tabulated age wise during and after treatment.

Height

A regular increase in height with age advancement was seen in all children as is shown in Table 1. The height of the children in the cohort was comparable to Agarwal standards (standards used for Indian children) but lesser than CDC standards at diagnosis. Mean $\pm$ SD of height during treatment was consistently on the lower side when compared with age matched controls for both boys and girls. During therapy, boys had lesser height gain which was insignificant except in the age group of 4–5 years ($p < 0.05$) in comparison to the Agarwal charts. However, the height of boys in the age group of 4–9 years was significantly less ($p < 0.05$) as compared to their American counterparts. Two years after completion of therapy, boys were shorter, but not significantly so, in comparison to Agarwal standards but were significantly shorter ($p < 0.05$) in the age group of 6.5–11 years when compared to CDC criteria. Girls had significantly less height in the 3–7 year age group ($p \leq 0.05$) in comparison to Agarwal and CDC standards during therapy. Two years after completion of therapy, girls in the age group of <9 years were significantly shorter ($p \leq 0.05$) by both Agarwal and CDC standards.

Height z scores decreased steeply during first 6 months of starting treatment and decreased further while on treatment followed by catch up after completion of therapy (Table 2; Fig. 1). The changes in height z scores however were not statistically significant ($p = 1$). The z score decreased steeply in both sexes during the first 6 months of therapy (-1.01). However, the decrease was greater in girls (-1.42) as compared to boys (-0.99) till completion of treatment. Catch up after completion was better in boys (-0.88 vs -1.32).

Weight

Weight of the study cohort was less as compared to Agarwal and CDC standards at all times periods of

Table 1 Comparison of height (cm) of subjects with Agarwal and CDC standards

Age (years)	Mean ht. of boys in study group during treatment (p-Agarwal/CDC)	Mean ht. Agarwal	Mean ht. CDC	Mean ht. of boys in study group after treatment (p-Agarwal/CDC)	Mean ht. of girls in study group during treatment (p-Agarwal/CDC)	Mean ht. Agarwal	Mean ht. CDC	Mean ht. of girls in study group after treatment (p-Agarwal/CDC)
2	86 (0.936/0.55)	85.6	89.1		83	85.7	87.73	
2.5	90.75 (0.851/0.506)	90.4	92.78		87.83 (.063/0.134)	90	81.82	
3	94.4 (0.753/0.231)	94.9	96.82		88.42 (.006/0)	94.1	95.75	
3.5	96.78 (0.120/0.039)	99.1	100.4		93.11 (.003/0)	97.9	99.67	
4	99.25 (0.002/0)	102.9	104	108	95.12 (.000/0)	101.6	103.5	
4.5	102.5 (0.002/0.001)	106.6	107.1	108	99.18 (.001/0)	105	105.98	99.83 (0.144/0.108)
5	104.31 (0.024/0)	107.1	110.9	109.55 (0.342/0.585)	101.45 (.001/0)	108.4	109.87	103 (0.036/0.017)
5.5	108.21 (0.133/0)	110.4	113.8	110.28 (0.949/0.068)	103.25 (.006/0)	109.4	113.77	107.5 (0.159/0.019)
6	111.54 (0.056/0)	113.7	117.2	113.40 (0.819/0.02)	110.72 (.172/.004)	113	116.46	107.9 (0.080/0.006)
6.5	115 (0.069/0.001)	117.5	120.1	115.24 (0.122/0.002)	113.25 (.323/.02)	115.4	119.3	110.5 (0.028/0.001)
7	117.22 (0.247/0)	118.6	123.4	117.74 (0.531/0)	116.38 (.374/.013)	118.2	122.52	113.18 (0.032/0.002)
7.5	121.08 (0.676/0)	121.6	126.6	119.37 (0.121/0)	118.43 (.460/.019)	120.2	125.27	116.04 (0.041/0.001)
8	122.37 (0.19/0)	124.1	128.6	124.27 (0.905/0.007)	123.5 (.840/.259)	122.7	128.29	119.7 (0.060/0)
8.5	125.61 (0.636/0.003)	126.4	131.5	126.09 (0.838/0.001)	127.14 (.764/.204)	126.2	131.41	121.82 (0.090/0.004)
9	126.65 (0.085/0.002)	130.4	134.7	129.49 (0.440/0)	132 (.472/.618)	128.6	134.3	127 (0.480/0.01)
9.5	131.83 (0.938/0.265)	131.5	136.9	130.94 (0.659/0)	131.9 (.807/.226)	131	136.83	130.43 (0.841/0.058)
10	132.5 (0.611/0.141)	134.7	139.5	132.47 (0.119/0)	135.5 (.918/.547)	134.8	139.85	133.44 (0.584/0.027)
10.5	137.25 (.923/0.2)	137.6	142.3	136.46 (0.470/0.002)	124	137.9	142.88	140.75 (0.414/0.537)
11	133.83 (0.114/0.016)	139.6	144.6	137.49 (0.370/0.007)	127	141.3	146.64	136.6 (0.360/0.092)
11.5	138.91 (0.234/0.016)	142.3	147.9	142.19 (0.955/0.008)	128	144.3	149.91	137.34 (0.005/0)
12	144.18 (0.774/0.004)	144.7	151.4	142.73 (0.596/0.041)	132	146.7	153.19	143.55 (0.338/0.023)
12.5	147.2 (0.794/0.039)	147.9	154.7	144.98 (0.340/0.006)		149.9	156.26	144 (0.378/0.121)
13	148.93 (0.740/0.084)	150.3	158.4	150.4 (0.967/0.005)		151.4	158.7	147.86 (0.316/0.019)
13.5	152.83 (0.672/0.192)	154.9	160.9	149.77 (0.090/0.002)		153.2	159.36	148.83 (0.548/0.226)
14	154.66 (0.439/0.081)	158	166.1	156.07 (0.523/0.012)		153.6	160.73	147.53 (0.384/0.138)
14.5	157	161.4	168.4	157.95 (0.280/0.005)		154.8	161.35	157.25 (0.835/0.734)
15		164.3	170.6	157.5 (0.178/0.029)		155	162.34	152.6 (0.622/0.144)
15.5		165.5	172.3	166.98 (0.732/0.244)		155.4	163.61	159.9 (0.470/0.532)
16		167.1	173.3	165.47 (0.834/0.371)		155.1	162.73	
16.5		167.9	175.6	167.12 (0.878/0.148)		156	162.37	167 (0.633/0.182)
17		168.6	175.7	169.94 (0.560/0.026)		157.1	162.83	154.9

p value not calculated where the numbers were less

Blank: no patients in that group

evaluation. Weight increased consistently with age but the children remained smaller in comparison to Agarwal and CDC criteria (Fig. 1; Table 3). On comparing with CDC standards, boys in the age group of 3–12 had significantly less weight at diagnosis and during therapy ($p \leq 0.05$) whereas on comparison with Agarwal standards, boys between 3–6 years had significantly less weight. After treatment boys had less weight when compared to the CDC standards in the 7.5–10 years group, being at par to the standards of Indian children. Girls had less weight during therapy in the age group of 3–5 years in comparison to

Agarwal & CDC standards ($p \leq 0.05$). After completion of therapy weight of the girls was significantly less when compared to the CDC standards in the age group of 5–10 years ($p < 0.05$). Weight z scores decreased during first 6 months of therapy but showed catch up thereafter. (Table 2; Fig. 1) This change of z scores was statistically significant for weight at end of treatment ($p = 0.032$) and 2 years after completion of treatment ($p = 0.00$). The gender wise comparison of weight z scores showed that catch up was better in boys as compared to girls. However, this change of z scores was statistically significant for boys

Table 2 Z scores for height, weight and BMI

Phase of study	Height, weight and BMI z scores																							
	All subjects								Boys				Girls											
	N		Height		Weight		BMI		N		Height		Weight		BMI		N		Height		Weight		BMI	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Induction	73	-0.81	1.23	-1.25	0.85	-1.2	0.92	52	-0.81	1.194	-1.32	0.89	-1.33	0.95	21	-0.71	1.49	-1.18	0.79	-0.95	0.81			
After 6 months	73	-1.04	1.13	-1.30	0.69	-1.08	0.75	52	-1.01	1.10	-1.26	0.75	-1.10	0.82	21	-1.01	1.39	-1.26	0.76	-0.79	0.8			
At end of therapy	73	-1.12	1.05	-0.84	0.845	-0.45	0.81	52	-0.99	1.05	-0.83	0.83	-0.54	0.73	21	-1.42	1.05	-0.91	0.81	-0.33	0.89			
At 2 years after completion therapy	73	-1.04	1.06	-0.66	1.05	-0.30	0.99	52	-0.88	1.05	-0.59	1.07	-0.31	1.01	21	-1.32	1.06	-0.80	0.77	-0.28	0.97

Fig. 1 Z scores for height, weight and BMI

at 2 years after completion of treatment when compared with induction ($p = 0.00$) and 6 months after therapy. This was not statistically significant for girls.

BMI

The BMI was compared to CDC standards. This decreased significantly in all ages during therapy for boys and only in a few age groups in girls. After therapy the BMI was still low in both sexes but was significant only in a few age groups (p 0.002, 0.034 at 9 and 14.5 years for boys and 0.014, 0.047, 0.037 at 9, 9.5, 13 years for girls) It was found to be in the normal range in boys but continued to be low in the girls in some age groups.

BMI z score increased throughout the study period (Fig. 1). This is probably because of a greater decrease and less catch up of height as compared to weight. This change was statistically significant for boys at the end of treatment (p 0.0) and 2 years after completion of therapy (p 0.0) but was not significant for girls at any point of time (Table 2; Fig. 1).

Table 3 Comparison of weight (kg) of subjects with Agarwal and CDC standards

Age (yrs)	Mean wt. of boys in study group during treatment (p-Agarwal/CDC)	Mean wt. Agarwal	Mean wt. CDC	Mean wt. of boys in study group after treatment (p-Agarwal/CDC)	Mean wt. of girls in study group during treatment (p-Agarwal/CDC)	Mean wt. Agarwal	Mean wt. CDC	Mean wt. of girls in study group after treatment (p-Agarwal/CDC)
2	11.15 (0.44/0.23)	12.3	13.13		10.3 (0.40/0.29)	11.8	12.47	
2.5	12.11 (0.05/0.04)	13.5	13.95		11.46 (0.01/0.001)	13	13.59	
3	13.01 (0.003/0.001)	14.6	15.08		11.82 (0.001/0)	14.1	14.65	
3.5	14.02(0.008/0.003)	15.7	16.2		12.9 (0.001/0)	15.1	15.57	
4	14.27 (0/0)	16.7	17.2	16	13.4 (0/0)	15.9	16.79	
4.5	15.28 (0/0)	17.7	18.11	18	14.31 (0.002/0)	16.8	17.63	14.6 (0.08/0.05)
5	15.94 (0.005/0)	17.4	19.49	18.46 (0.4 8/0.48)	15.12 (0.029/0)	17	18.97	16.16 (0.18/0.006)
5.5	16.98 (0.005/0)	18.4	20.47	18.6 (0.76/0.06)	15.41 (0.015/0)	17.9	20.53	17.06 (0.006/0)
6	18.08 (0.03/0)	19.2	21.56	19.54 (0.62/0.07)	17.71 (0.27/0.002)	18.7	21.11	17.8 (0.35/0.006)
6.5	19.65 (0.11/0)	20.6	22.92	21.28 (0.61/0.23)	18.82 (0.56/0.035)	19.6	22.16	18.85 (0.35/0.006)
7	19.63 (0.08/0)	21	24.07	22.18 (0.30/0.1)	19.52 (0.38/0.005)	20.5	23.58	19.97 (0.74/0.05)
7.5	21.23 (0.109/0)	22.4	25.58	21.96 (0.6/0.001)	22.02 (0.818/0.05)	21.7	25.04	20.2 (0.10/0)
8	21.9 (0.015/0)	23.5	26.43	24.50 (0.52/0.22)	21.4 (0.53/0.078)	23	26.64	23.36 (0.76/0.018)
8.5	23.83(0.54/0.001)	24.5	28.46	25.36 (0.49/0.02)	23.8 (0.38/0.007)	24.9	28.59	24.65 (0.89/0.06)
9	22.98 (0.016/0)	26.5	30.55	26.08 (0.66/0)	27.9 (0.49/0.39)	25.8	30.59	25.02 (0.54/0.002)
9.5	24.9 (0.46/0.03)	26.8	31.86	28.44 (0.23/0.02)	26.76 (0.78/0.07)	27.5	32.74	26.8 (0.74/0.029)
10	25.55 (0.15/0.008)	28.7	33.47	28.71 (0.98/0.001)	29.13 (0.95/0.53)	29.6	34.02	28.6 (0.53/0.006)
10.5	26.13 (0.026/0.001)	30.8	36.06	31.82 (0.59/0.04)	24.4	31.9	35.72	33.86 (0.51/0.53)
11	27.85 (0.015/0)	31.9	37.61	31.78 (0.95/0.01)	26.4	34.3	39.28	30.2 (0.19/0.02)
11.5	29.7 (0.063/0.002)	33.8	40.39	36.62 (0.24/0.12)	28.8	36.8	42.37	32.42 (0.038/0.001)
12	33.20 (0.228/0.001)	35.4	42.07	36.08 (0.85/0.12)	29.8	38.7	44.89	37.95 (0.81/0.06)
12.5	35.24 (0.55/0.079)	37.9	44.89	39.02 (0.72/0.08)		41.9	47.88	42.02 (0.98/0.47)
13	33.67 (0.37/0.04)	39.4	47.94	44.60 (0.05/0.3)		42.6	50.49	38.51 (0.178/0.006)
13.5	42.26 (0.88/0.24)	43.2	51.69	42.70 (0.89/0.03)		45.2	51.64	49.73 (0.64/0.84)
14	43.8 (0.88/0.169)	44.7	54.97	46.88 (0.7/0.19)		45.7	53.78	41.46 (0.55/0.17)
14.5	44	48.1	57.9	46.575 (0.56/0.01)		46.6	55.1	56.1 (0.60/0.95)
15		51	59.48	48.94 (0.59/0.03)		48	55.22	46.1 (0.67/0.14)
15.5		52.4	62.65	52 (0.93/0.03)		48.9	56.96	62.72 (0.30/0.56)
16		55	64.63	50.46 (0.65/0.25)		49.2	57.36	
16.5		54.9	67.83	57.78 (0.67/0.19)		49.6	57.7	60
17		56.6	67.64	61.52 (0.33/0.24)		49	58.23	50.9

p value not calculated where the numbers were less

Blank: no patients in that group

Growth Velocity

Growth velocities were computed in this cohort of children. Peak weight velocity occurred at 13 years for girls (4.63 kg/year) and 14 years for boys (6.28 kg/year). This was late and higher in comparison to standards for Indian children [5] where it occurs at 11.5 years for girls (4.6 kg/year) and 13.5 years for boys (3.7 kg/year). Peak height velocity occurred at 13 years for girls (5.77 cm/year) and 14 years for boys (6.09 cm/year). This was again late in comparison to standards for Indian children [5] where it occurred at 11.5 years for girls (5.4 cm/year) and

12.5 years for boys (6.4 cm/year). There was no significant difference in growth velocities between both sexes.

Discussion

Our study was done to look for the effect of treatment of ALL on growth. Studies from the developed countries have shown that children have deceleration of growth in the initial phase of therapy, followed by catch up growth. However, reports have been conflicting essentially owing to (i) different eras of studies (ii) differences in the

chemotherapeutic regimens (iii) different age groups being studied (especially when pubertal age group is studied) and (iv) inclusion of CRT in the patients.

We have observed a deceleration of height throughout therapy, this being maximum in the first 6 months of therapy. Catch up growth was observed after completion of therapy. However, children were still shorter than the age norms even 2 years after completion of therapy. This would possibly be attributable to CRT and chemotherapy per se. CRT has an effect on growth hormone regulation with GH deficiency being the most common endocrine problem after CRT. In addition, intense chemotherapy is also known to directly affect the epiphyseal growth plates. Maintenance therapy is also implicated in inhibition of short term growth secondary to myelosuppression.

The effect of therapy on growth retardation was observed in the late eighties. CRT was considered a major factor for growth retardation. Subsequently various authors have reported an initial slowing of growth during the intense phase of therapy followed by a gradual catch up. The dose of CRT, the absence of CRT were studied variously for effect on growth slackening [7, 8]. Comparable observations were found by different studies where they found that height SDS scores decreased during treatment, the decline being more in the first year after starting treatment [1, 2, 9–12]. This has been noted in children who received CRT as well as those who did not receive CRT, the effect being more in the children who received CRT [3, 8, 11–16]. Catch up growth was seen to occur soon after completion of therapy. Authors have reported catch up to occur even 5–6 years after completion of therapy.

The weight z scores decreased during first 6 months of therapy and showed a catch-up subsequently. All children remained smaller as compared to norms throughout treatment and after completion of therapy. Approximately 1/3rd of our children are underweight at admission (Unit statistics). Studies from developing nations report underweight to be seen at diagnosis in children with a malignancy, to range between 20–57 % [17]. The National Family Health Survey 3 in India, reports that in children under 5 years of age 48 % are stunted and 43 % are underweight [18]. In a developing country it is expected to have children with lower weight emphasizing the need for nutritional support.

Jaruratanasirikul et al. found that weight z scores increased slightly from diagnosis to end of treatment but showed a decrease thereafter over 6 years after treatment [13]. Müller et al. observed that during follow-up long term survivors of childhood ALL developed an increase in weight for height index [14]. Davies et al. established that nearly half the children were obese at final height, with no significant difference in incidence between the sexes [19]. In comparison, though our children had an increase in weight after completion of therapy, no child was noted to

be obese and they were lighter in comparison to CDC and Agarwal standards.

On evaluation of peak growth velocities in our cohort, velocity for weight showed a peak at 13 years for girls (4.63 kg/year) and 14 years for boys (6.28 kg/year). This was late and more in comparison to standards for Indian children [5] where it was seen to occur at 11.5 years for girls (4.6 kg/year) and 13.5 years for boys (3.7 kg/year). There was no significant difference in velocities between boys and girls.

BMI of both boys and girls was seen to be less while on therapy as compared to the CDC norms. The BMI was seen to be higher when off therapy as compared to whilst on therapy. This change was significant in boys ($p = 0$ at end of treatment and 2 years after completion of therapy) but not so in girls ($p = 1$ at end of treatment and 2 years after completion of therapy). Most authors have reported an increase in BMI during and after therapy [3, 4, 16, 20–23]. ALL survivors have also been seen to have a greater tendency to be overweight which has been observed to be more in the patients who received CRT. The increase of BMI in our cohort could be attributed to the greater impact of treatment on height as compared to weight as our patients always had weight on the lower side of normal.

Conclusions

Children have affectation of growth, especially height, during therapy for ALL. There is catch up growth after the intense phase. Despite catch up growth the children remained smaller than the norms for age. The BMI has increased consistently but no child was seen to be overweight. Peak of height and weight velocity occurred late in our patients. However, we have not evaluated the final height in this cohort of patients. This would be possible after a period of time when they have achieved their final adult height.

Conflict of interest The authors state no conflict of interest in this manuscript.

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