Growth & pubertal patterns in young survivors of childhood acute lymphoblastic leukemia

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Background

- Acute lymphoblastic leukemia (ALL) is the most common childhood cancer.
- Both chemotherapy & radiotherapy have serious potential side effects, especially when used in children.
- The endocrine system is especially prone to secondary treatment-induced injury, and a variety of endocrine abnormalities may develop in survivors of childhood ALL.

Objective

- To evaluate growth & pubertal patterns in patients diagnosed with childhood ALL.
- To identify risk factors for impaired growth & puberty.

Patients & Methods

Study design: A retrospective chart review with longitudinal assessment of anthropometric measurements & pubertal status of childhood ALL survivors diagnosed between 1985 & 2011.

- **Inclusion criteria:** Age 8-30 years at data collection
  Continuous first complete remission
  Follow-up ≥3 years since diagnosis.
- **Exclusion criteria:** Death/disease recurrence
  Hematopoietic stem cell transplant
  Syndromes associated with impaired growth.

Data collected from medical charts:

- ✓ Demographic parameters
- ✓ Chemotherapy & radiotherapy exposure
- ✓ Age of pubertal onset; Menarche & menstrual regularity (females)
- ✓ Occurrence of endocrine complications
- ✓ Use of hormone replacement therapy (GH, sex-hormone, etc.)
- ✓ Parental height
- ✓ Anthropometric measurements; Assessment of pubertal stage

Evaluated potential risk factors for adverse endocrine outcome:

- **Gender**
- **Patient age and pubertal stage at diagnosis**
- **Cranial irradiation (yes/no),**
- **Type of chemotherapy protocol**

Results

Characteristics of childhood ALL survivors

Characteristics	Entire ALL cohort (n=183)	chemotherapy +cranial Irradiation (n=29)	chemotherapy alone (n=154)	p
Males/females, n (%)	88/95 (48.1/51.9)	19/10 (65.5/34.5)	69/85 (44.8/55.2)	0.041
Ethnicity, n (%)				
Ashkenazi-Jews	29 (15.8)	2 (6.9)	27 (17.5)	
Sephardi-Jews	74 (40.4)	10 (34.5)	64 (41.6)	NS
Arabs	26 (14.2)	3 (10.3)	23 (14.9)	
Combined ethnicity	54 (29.6)	14 (48.3)	40 (26)	
Age at diagnosis (yr)	5.7 (3.5, 8.8)	7.5 (3.9,11.2)	5.7 (3.3, 8.6)	NS
Chemotherapy protocol n (%)				
INS 84	19 (10.4)	12 (41.4)	7 (4.5)	
INS 89	25 (13.7)	7 (24.1)	18 (11.7)	<0.001
INS 93	35 (19.1)	3 (10.3)	32 (20.8)	
INS 98	45 (24.6)	2 (6.9)	43 (27.9)	
INS 2003/2007	59 (32.2)	5 (17.3)	54 (35.1)	
Age at last visit (yr)	16.1 ± 3.9	18.2 ± 3.6	15.7 ± 3.8	0.001
Duration of follow-up (yr)	8.7 (6.8, 12.2)	10.5 (7.2, 13.6)	8.6 (6.4, 12.1)	NS
Height-SDS at diagnosis				
Males	-0.16 (-0.61, 0.71)	-0.33 (-0.68, -0.15)	-0.03(-0.58, 0.83)	NS
Females	0.15 (-0.59, 0.78)	0.32 (-0.18, 1.09)	0.13 (-0.62, 0.78)	
BMI-SDS at diagnosis				
Males	-0.04 (-0.98, -1.05)	-0.24 (-1.32, 1.03)	0.09 (-0.98, 1.08)	NS
Females	0.26 (-0.53, 1.16)	0.34 (-1.90, 1.48)	0.21 (-0.52, 1.15)	
Height-SDS last visit				
Males	-0.52 ± 1.14	-0.97 ± 1.0	-0.39 ± 1.15	0.037
Females	-0.14 ± 0.96	-0.83 ± 0.77	-0.06 ± 0.95	0.012
BMI- SDS last visit				
Males	0.41 (-0.47, 1.35)	-0.10 (-0.98, 0.85)	0.70 (-0.43, 1.38)	NS
females	0.40 (-0.34, 1.15)	0.13 (-0.91, 1.17)	0.48 (-0.32, 1.16)	NS
Final height-SDS last visit				
Males	-0.44±1.11	-0.84±1.09	-0.29±1.09	NS
Females	-0.29±0.91	-0.87±0.82	-0.20±0.89	0.049
Pubertal stage at last visit, n (%)				
Tanner 1	16 (8.9)	1 (3.4)	15 (9.7)	
Tanner 2	13 (7.2)	2 (6.9)	11 (7.1)	NS
Tanner 3	22 (12.2)	2 (6.9)	20 (13)	
Tanner 4	16 (8.9)		16 (10.4)	
Tanner 5	113 (62.8)	23 (79.3)	90 (58.4)	
Age at initiation of puberty, (yr)				
Males	12.0 (11.2, 13.1)	13.1 (12.2, 13.6)	12.0 (11,12.6)	0.016
Females	10.0 (9.8-11.0)	10.0 (9.5,11.3)	10.0 (9.9, 11)	NS
Age at menarche, (yr)	12.0 (11.7, 13.1)	12.0 (11.0, 13.2)	12.0 (11.7, 13.0)	NS

Data are expressed as mean ± standard deviation (SD) for normally distributed variables and median (interquartile range) for skewed variables.
Data about age of onset of puberty was available for 103 patients, and data about menarche was available for 62 females.
P value is between patients treated with adjuvant cranial irradiation and those treated with chemotherapy-alone.

Endocrine disturbances of ALL survivors

	Entire ALL cohort (n=183)	chemo+ cranial irradiation (n=29)	chemotherapy alone (n=154)	*P*
GH deficiency	5 (2.7)	3 (10.3)	2 (1.3)	0.029
Precocious puberty	16 (8.7)	4 (13.8)	12 (7.8)	NS
Hypothyroidism (primary)	2 (1)	1 (3.4)	1 (0.6)	NS
Hypogonadotrophic hypogonadism	2 (1)	1 (3.4)	1 (0.6)	NS
Short stature (Height-SDS≤ -2SD)	9 (4.9)	2 (6.9)	7 (4.5)	NS
Obesity (BMI-SDS ≥ 1.645 SD)	17 (9.3)	3 (10.3)	14 (9)	NS
Overweight (BMI-SDS =1.036–1.644 SD)	42 (23)	3 (10.3)	39 (25.3)	0.032

Data are expressed as number (%). P value is between patients treated with adjuvant cranial irradiation & those treated with chemotherapy alone.

Predictors of endocrine disorders in childhood ALL survivors

Variable	B	S.E.	OR	95% CI	*P*
Obesity					
BMI-SDS at diagnosis	0.378	0.109	1.46	1.18- 1.81	0.001
Short stature					
Age at diagnosis	0.481	0.328	1.62	0.85- 3.08	0.143
Ht-SDS at diagnosis	-1.047	0.503	0.35	0.13- 0.94	0.038
Other endocrine disorder					
Age at diagnosis	-0.188	0.103	0.83	0.68- 1.02	0.069
Gender	1.180	0.578	3.26	1.04- 10.1	0.041
Cranial irradiation	1.375	0.637	3.96	1.14- 13.78	0.031

OR denotes odds ratio; CI denotes confidence interval.
The regression analysis included the following parameters:
- Gender (females vs. males)
- Age at diagnosis
- Tanner stage at diagnosis (Tanner 2-5 vs. Tanner 1)
- Type of chemotherapy protocol (INS 84 & 89 vs. INS 93 & 95 and 2003/2007)
- Use of cranial irradiation (irradiation vs. no irradiation).

For prediction of obesity the analysis included also the BMI-SDS at diagnosis

For prediction of short stature the Height-SDS at diagnosis & the midparental height were included.

Final Height

Adult height was attained in 115 patients (62.8%) from the study cohort at their last visit.
In these patients, short stature was found in 13% of patients treated with chemotherapy + cranial irradiation & in 2.2% of patients who were treated with chemotherapy-alone.

Puberty

The occurrence of **precocious puberty** was higher in girls who got cranial irradiation vs. those treated with chemotherapy-alone (30% vs. 9.4%).

Conclusions

- Although most patients treated with chemotherapy-alone attained normal adult height & puberty, those treated with adjuvant cranial irradiation are at increased risk for short stature and precocious puberty (in girls).
- Hopefully, with recent treatment with reduction of radiotherapy doses or replacement of radiotherapy by intensive chemotherapy, the prevalence of impaired final height and other endocrine disorders in these survivors will further decrease.
- Childhood ALL survivors are at an increased risk for overweight, especially those with increased BMI at diagnosis. Therefore, clinicians need increased awareness & screen for overweight & its associated health conditions early in survivorship. Interventions as changes in lifestyle habits are required to address weight control early during treatment.

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