Impact of treatment on the growth of children treated for acute lymphoblastic leukemia

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Abstract

Background: Endocrine disturbances are frequent long-term complications of acute lymphoblastic leukemia (ALL) treatment. Research on the risk of impaired linear growth and overweight has reported conflicting results. Procedure: A longitudinal, retrospective study for the characterization of growth (height and body mass index (BMI)) was performed, based on the clinical records of patients treated for ALL since 2003 and off treatment for a minimum of two years. Data on height and weight were collected at diagnosis (0M) and at 6, 12, 24 and 48 months (M), as well as the most recent height (FH). Effects of cranial radiotherapy (CRT) and sex on growth changes were evaluated. FH was compared with target height (TH). Results: 78 patients (52.5% males) met the inclusion criteria. CRT was used in 28.2%. Height percentile (HP) was reduced at 6M reaching a minimum at 12M; this recovered at 48M, but was still inferior to diagnosis for females and most significantly in the CRT group. Diagnosis HP was in general higher than TH. Overweight/obesity affected 21.8% patients at 0M, 45.9% at 12M and 71.4% at 24M. BMI percentile (BP) decreased from 24M to 48M but was still higher than at 0M. The CRT-group had no significant decrease in BP from 24M to 48M. Conclusions: ALL treatment affected linear growth and caused an increase in BMI, with a higher impact on CRT-treated patients for both studied parameters and in females only for height. FH appeared not to be inferior to patient's genetic potential. BMI remained increased after treatment.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood and accounts for 80% of all leukemia cases in children.[1] Recent progress in treatment for childhood ALL, including risk-directed treatment, has resulted in 5-year overall survival rates above 85%.[2,3] Attention must be given to late side effects of the treatment, including increased cancer survivors' morbidity and premature death. Long-term monitoring of survivors has therefore become a relevant part of their overall health care.[4]

Endocrine disturbances are frequent long-term complications of ALL treatment. The increased risk of impaired linear growth and obesity/overweight has been largely studied over the past decades to determine whether these adverse outcomes are predictable and potentially reversible.[5-12, 14-24] Published results are conflicting and, in some cases, difficult to interpret considering the heterogeneity of therapeutic protocols in use. In recent decades, cranial radiotherapy (CRT) has mostly been replaced by intrathecal chemotherapy as the standard central nervous system prophylaxis and treatment, resulting in less sequelae related to this treatment modality.[3] Nevertheless, even chemotherapy alone has been suggested to negatively affect growth and endocrine functions.

Height deficit during treatment is a common finding in children treated for ALL.[5] Many studies further suggest that adult survivors of ALL have long-term impaired growth and decreased final height (FH)[5-7], while others find that FH is not significantly affected by treatment.[8-10] Different studies found this effect on

linear growth to be more pronounced or only significantly seen in some subgroups such as patients treated with CRT,[7,8,11] females[12] or younger children.[7] When addressing height after treatment, most published studies compare height percentiles (HP) or standard deviation-scores (SD) with general population height patterns and with patient's height at the time of diagnosis. This approach does not take into account the so-called "genetic potentiality", usually evaluated by the target height (TH), which can be estimated from parent's height.[13]

Excessive increase in body mass index (BMI) is another known effect of ALL treatment. [5,14] This increase may persist for several years after treatment completion.[15-17]Age,[18,19] sex,[5,15,20] therapeutic regimen (use of CRT,[11] type of glucocorticoids[15]) and BMI at the time of diagnosis[8,15,17,19,21] are some of the studied risk factors for obesity/overweight in ALL survivors.

Increased adiposity is associated with important metabolic abnormalities, such as insulin resistance and dyslipidemia, resulting in increased cardiovascular risk and mortality. Early identification of endocrine and metabolic disturbances is crucial in order to implement effective interventions to prevent these risks and improve patients' health and quality of life. [22-24]

Our study aims to characterize the growth of children and adolescents treated for ALL in terms of height and BMI, during and after treatment, testing for possible effects of CRT and sex on growth changes and comparing height after treatment with TH, i.e., with patient's genetic potentiality.

Methods

- Design and setting

A longitudinal, retrospective study was performed. It comprised evaluation of clinical records of all patients aged between 1 and 18 years old treated in our center since 2003 for ALL or lymphoblastic lymphoma (LL) according to the Dana-Farber Cancer Institute (DFCI) Protocols (DFCI 95-01 from 2003 until 2005, DFCI 00-001 in 2006 and DFCI 05-01 from 2007 until 2013) and off treatment for more than two years. Inclusion criteria included the successful completion of treatment and continued first remission. Exclusion criteria included: death, relapse, use of other treatment protocols, lost to follow-up and lack of data. Details concerning the DFCI treatment protocol have been published elsewhere[25] and are summarized in **Table 1** .[27]

Ethical guidance was followed throughout the study and included informed consent for patients and families.

- Data collection

Height and weight were extracted from the record of each eligible patient at different time points relative to the time of diagnosis: at diagnosis (0M) and at 6 months (6M), 12 months (12M), 24 months (24M) and 48 months (48M) after diagnosis and the beginning of treatment. Most recent/last height measurement (LH) was also registered. Parental height was also collected to estimate TH, calculated according to the formula: (mother's height + father's height + 13)/2 in males and (mother's height + father's height - 13)/2 in females. Uniformly, height was measured to the nearest cm with a wall-mounted stadiometer; body weight was measured to the nearest 0.1 kg. The auxological instruments were routinely checked and calibrated. BMI was obtained from weight in kg/height in square meters. Height and BMI were converted to percentiles using age- and sex- specific World Health Organization Growth Chart 2007.[26] For each participant, demographic and therapeutic information was obtained, including gender, age at diagnosis, treatment risk group[27] and use of CRT.

- Data analysis

All results, apart from ages expressed by median, were reported as the mean ± SD. Statistical analysis was performed using SPSS21®. All quantitative variables were firstly tested for normality. For variables with normal distribution, parametric statistical analysis was performed using dependent sample Student's t-test.

Nonparametric statistical analysis was performed on the other variables using dependent sample Wilcoxon

matched-pairs test or the Friedman test. Bonferroni correction was performed before comparing paired samples. A P-value below 0.05 was considered statistically significant.

Results

Among 108 patients treated since 2003 in our center and off treatment for a minimum period of two years, 78 met the inclusion criteria. Causes of exclusion included: death (11.1% of initial population), use of other treatment protocol (10.2%), relapse (2.8%), lost to follow-up (1.8%) and lack of data (1.8%).

The final study sample of 78 patients comprised 41 males (52.6%) and 37 females (47.4%). Ages ranged from 1.2 to 17.4 years at time of diagnosis, with a median of 6.3. ALL was the diagnosis for 97% of the cases and LL for 3%. According to risk stratification categories, patients were classified as standard risk (SR) in 54%, high risk (HR) in 39% and very high risk (VHR) in 8%. CRT was used in 28% of all patients, in 9.5% of SR, 43% of HR and all but one VHR patients. Therapy in DFCI protocols has changed over time. One of the major changes was in CRT which was indicated for all the in the 95-01 protocol, which justifies the percentage of irradiated patients.

Height

Absolute values of mean, SD, minimum and maximum height for the whole sample, by gender and according to treatment with or without CRT, evaluated at 0M, 6M, 12M, 24M and 48M after diagnosis are shown in**Table 2** . **Table 3** displays HP distribution throughout the study period. **Table 4** compares HP among different time points of assessment for the general sample, by gender and between those with and without CRT.

In the whole population, a significant reduction of HP was documented at 6M after diagnosis ($p<0.001$ for 0M vs 6M), with almost null linear growth throughout this period. The minimum HP is reached at 12M. From 12M on, height increase restarts, with a statistically significant recovery at 48M ($p=0.009$ for 12M vs 48M). HP at 48M, as well as LH percentile, are still considerably inferior to HP at diagnosis ($p<0.001$ for 48M vs 0M and for LH vs 0M).

However, HP at diagnosis is higher than TH percentile diagnosis ($p<0.001$ for 0M vs TH). Therefore, when comparing 48M and LH percentile with TH percentile, no statistically significant difference is observed ($p=0.129$ for 48M vs TH and $p=0.345$ for LH vs TH).

For both genders, as observed for the whole sample, a significant decrease in HP was observed during treatment and LH percentile is still inferior to HP at diagnosis. Nevertheless, a significant decrease from initial (0M) to final (48M) HP was documented for females ($p<0.001$) but not for males ($p=0.095$). Comparing HP at 48M with TH percentile for males, a higher value was noted for 48M ($p=0.021$), whereas for females no significant difference was found ($p=0.904$).

Comparing linear growth of patients who were submitted to CRT or not, both groups showed reduced growth during treatment and HP at 48M and LH considerably lower than those at diagnosis, but the difference between final and initial HP was significantly higher for the first group ($p=0.02$). For the patients who were not submitted to CRT, there was a significant growth from 24M on ($p=0.03$ for 12M vs 24M, $p=0.006$ for 12M vs 48M and 0.012 for 12M vs LH). This pattern of recovery is not seen for patients who underwent CRT. When comparing HP at 48M or LH with TH percentile, for the group with CRT no statistically significant difference was found ($p=0.214$ for 48M vs TH and $p=0.075$ for LH vs TH); for the group without CRT, the HP at 48M and LH percentile were higher than TH percentile ($p=0.01$ for 48M vs TH and $p=0.022$ for LH vs TH).

BMI

Absolute values of mean, SD, minimum and maximum BMI for the whole sample, by gender and according to treatment with or without CRT, evaluated at 0M, 6M, 12M, 24M and 48M after diagnosis and beginning of treatment are shown in **Table 5** . **Table 6** displays BMI percentile distribution throughout the study period.

At diagnosis, absolute mean values for BMI were 16.9 cm/m^2 for the whole sample (with a range from 12.2–29.7 cm/m^2), 17.3 cm/m^2 for males and 16.5 cm/m^2 for females. This difference between genders was not statistically significant (p=0.596). 1.3% of patients were underweight (BMI<P_3) and 21.8% of patients were overweight (BMI P_{85}-P_{97}) or obese ([?] P_{97}) at 0M.

BMI percentile was not significantly different between genders or between those submitted and those non-submitted to CRT for all measurements (**Supplemental Table S1**). **Supplemental Table S1** also demonstrates comparison of BMI Percentile among different time points of assessment for the general sample. A statistically significant increase in the BMI percentile was documented from 0M to 12M and a further increase from 12M to 24M (p<0.001 for comparison 0M vs 12M, 0M vs 24M, 6M vs 12M, 12M vs 24M). Overweight/obesity affected 45.9% and 71.4% of patients at 12M and 24M, respectively. BMI at the end of treatment was significantly higher than BMI at diagnosis (p<0.001 for 48M vs 0M), although there was a statistically significant decrease from 24M to 48M ((p<0.001 for 48M vs 0M). At 48M, 52.6% of patients were overweight or obese. The same pattern of increase continued until 24M and a decrease in BMI percentile from 24M to 48M was observed for female and male groups, with no statistically significant differences between groups. For patients with and without CRT, the same increase in BMI was observed from 0M and 6M to 12M and from 12M to 24M for both groups, but no significant decrease was observed from 24M to 48M in patients who underwent CRT.

Discussion

This study examines growth outcomes in a wide cohort of Portuguese survivors from childhood ALL.

Linear growth impairment has frequently been reported as a complication of ALL treatment.[5-12,28-30,33-37] Our study suggests a significant growth impairment which is already noticeable 6M after the beginning of treatment with a minimum HP reached at 12M, confirming a previously reported early detrimental effect of the treatment on height.[12,28]

Our data further characterize linear growth throughout the treatment period, showing a persistence of the impact on height until the end of treatment as no significant catch-up growth could be found until 24M after diagnosis. A significant recovery of linear growth started only at the end of treatment, at 48M after diagnosis, as documented by other reports.[12,29,30]

Data on long-term catch-up growth vary among previously published studies. While some authors report a decreased FH[29], others found no significant effect and a normal FH in survivors of pediatric ALL. [8-10,30]

We observed a final HP (inferred from height at 48M and LH) that was lower than HP at diagnosis, but not significantly different from target HP, i.e., the HP measured according to the individual genetic potential. Therefore, we should not assume that FH was effectively affected by the treatment, as the initial height could be higher than expected for the genetic potential.

The finding of relative increased height at diagnosis in children with ALL was also suggested by other reports.[28,31] Huang and Ducore reviewed 883 cases of pediatric oncologic patients and observed that ALL patients were taller than those with other cancers and than the global population of American children. The reason for this apparent height increase is unknown and may be related to growth changes seen in these children such as increased birth weight.[31]

A variety of factors have been implicated in growth impairment in children treated for ALL. Patients who received CRT seem to be more affected, as reported by many authors,[7,11] even with low-dose CRT.[32] Our data confirm this effect as the group of patients treated with CRT showed a greater impact on growth when compared with the group without CRT – they not only had a greater difference between final and initial HP but also did not experience the catch-up growth after treatment seen in those treated without CRT. This has been associated with radiation effects on the hypothalamic-pituitary axis, affecting growth hormone secretion.[11,33]

Other reports found no relevant impact of CRT on growth.[28]

Data on growth of patients treated with chemotherapy alone are less numerous and are discordant. While some studies report no effect on linear growth[8], others concluded that even children who were treated solely with chemotherapy also had significant height loss.[6,29] Bruzzi et al. demonstrated significant height loss compared to height SD at diagnosis and this loss persisted when adjusted according to TH. This report suggested genetic potential and growth pattern before ALL as the two main factors influencing FH.[5] How chemotherapy affects growth is still unclear, but an altered growth hormone (GH) secretion as well as well as catabolic effects caused by both ALL and its treatment have been suggested.[5] Females have been reported to be more affected than males.[5,34,35] Our results support this assertion, as a significant decrease of HP from diagnosis to 48M was documented for females but not for males. Other studies found no effect of gender.[29]

Other suggested risk factors for FH deficit are lower age at diagnosis, especially for patients younger than four years.[7,28,29,35,36,37] In contrast, Elitzur et al. reported older age at diagnosis as a predictor of impaired growth.[8]

Increased obesity has been pointed to as the most common late effect of ALL treatment. This has been associated with many factors, such as lifestyle modifications (increased energy intake and reduced habitual physical activity), radiotherapy-induced hypothalamic damage leading to hormonal deficiency and hypothalamic dysregulation of food intake control, chemotherapy, GH deficiency, corticosteroids and other hormone imbalances (such as leptin).[38]

All of these changes that occur along the treatment period lead to an increase in adiposity that is most commonly evaluated through BMI measurement.

Most reports are consistent with an increase in BMI during treatment. The first year of treatment is documented to be the period of most marked excess weight gain.[17,39] Some studies support high BMI at diagnosis and early weight gain during treatment as risk factors for obesity after end of treatment.[17,21]Relative height loss, apart from weight gain, is also a contributive factor to this BMI increase.[28]

Our results show an increase in the BMI percentile after one year of treatment and a further increase during the second year after diagnosis. The percentage of overweight or obese patients more than doubled at 12M (an increase from 21.8% to 45.9%) and triplicated at 24M after diagnosis (71.4%). Some studies reported similar increases.[14] Persistence of BMI increase after treatment is a more variable finding, but there is good evidence in favor of a maintenance of BMI increase beyond completion of the treatment.[16] Iughetti et al. reviewed studies analyzing the long-term prevalence of obesity in childhood after the end of ALL treatment and found a wide range of results, from 16% to 57% at 3 or 4 years after diagnosis. However, interpretation of the published data was difficult due to differences in treatment protocols, definitions of excess weight gain (use of different reference data), relatively small sample sizes and because some studies analyzed weight changes in children treated with both CRT and combination chemotherapy and others did not.[38]

In our study, although there was a decrease in the BMI percentile after the end of treatment (from 24M to 48M after diagnosis), with a reduction on the proportion of overweight/obesity to 52.6%, the increase in BMI percentile persisted significantly at four years after diagnosis.

Our data showed no significant differences between female and male groups in respect to the BMI trajectory during treatment and afterwards. The same result has been obtained by other authors,[16]while others have reported that females tend more to a persistence of an increased BMI after treatment than males.[20]

Concerning CRT-treated vs non-CRT-treated patients, both groups showed a similar increase in BMI throughout treatment, but only the second group experienced a significant decrease of BMI percentile after treatment. This is consistent with findings supporting the role of chemotherapy as a major factor for weight gain during treatment for ALL.[37,38] CRT has been shown to predispose patients treated for ALL to obesity.[11,22] However, although they concluded this increased risk of obesity, Siviero-Miachon et al. observed no association between CRT and BMI.[22] Zhang et al. documented unhealthy weight gain occurring regardless of patients' receiving CRT.[16]

Increased overweight and obesity in these patients is an important concern as it is accompanied by car-

diometabolic and endocrine alterations that increase morbidity and are responsible for relevant mortality in survivors of childhood ALL. Early intervention on improvement of nutrition, physical activity and other behavioral aspects, as well as further research on therapeutic agents-related toxicity, are crucial for better quality of life and long-term reduction in mortality of childhood ALL survivors.[22-24]

Conclusion

Our study supports the previously described impact of ALL treatment on the linear growth of children and adolescents during treatment. However, FH was substantially affected only for female patients and for those submitted to CRT, as also reported by other authors. Another interesting finding was a relatively higher HP at diagnosis of ALL patients when compared to target HP.

Regarding BMI percentile, an early and significant increase was found throughout the whole period of treatment. After treatment, a decrease in BMI percentile was seen, except for CRT-treated patients. Nevertheless, increased BMI persisted at four years after diagnosis. Results did not vary with gender. Therefore, dietary and behavioral interventions, as well as further research on therapeutic agent-related toxicity, are needed for a better quality of life and long-term reduction in mortality of childhood ALL survivors.

Conflict of Interest statement

The authors state no conflicts of interest.

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