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Pediatric Oncology

Alterations in Bone Turnover during Chemotherapy in Children with Acute Lymphoblastic Leukemia

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Abstract

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Background Disturbances of bone metabolism frequently occur in children with acute lymphoblastic leukemia (ALL), leading to increased risk of osteopenia and osteoporosis at diagnosis, during and after completion of chemotherapy. The present study was performed to evaluate alteration in bone mineral metabolism in children with ALL during chemotherapy.

Method Fifty newly diagnosed patients with ALL in the age group of 2 to 14 years were included. Relapsed and refractory cases were excluded. Enrolled children were stratified into standard and high risk according to National Cancer Institute criteria. Quantitative analysis of bone resorptive marker carboxyl-terminal telopeptide of human type 1 collagen (ICTP) was assessed at baseline and 3 months after chemotherapy by the sandwich enzyme-linked immunosorbent assay technique.

Results Of 50 patients enrolled, 21 were standard and 29 were high risk. The mean age was 7.75 ± 4.0 years and the male-to-female ratio was 3.5:1. ICTP levels were analyzed in 44 patients, of which 37 (84%) showed significantly increased levels. The mean ICTP level in patients at diagnosis and controls was 1.78 ± 1.39 and 0.96 ± 0.32 μg/L, respectively ($p = 0.001$). The mean ICTP level at 3 months after chemotherapy increased to 3.55 ± 1.40 μg/L ($p = 0.000$). It was significantly increased in males ($p = 0.000$) and in B cell ALL group ($p = 0.000$) in comparison to females and T cell group. Both standard and high risk groups were equally affected ($p = 0.000$). On multivariate analysis, no single risk factor could be identified.

Conclusion The marker of bone resorption (ICTP) in children with ALL was increased at diagnosis, which further increased during chemotherapy. The disease itself and the intensive chemotherapy both contributed to the increased levels.

Keywords
- skeletal morbidity
- acute lymphoblastic leukemia
- bone metabolism
- carboxyl-terminal telopeptide of human type 1 collagen (ICTP)
- quality of life

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Introduction

Acute lymphoblastic leukemia (ALL) is the commonest childhood malignancy. Advancement in the treatment regimen of ALL has not only increased the survival rate but also the late effects of the disease and its treatment. Out of several morbidities, skeletal morbidity is increasingly being recognized in ALL patients and may result in fractures, pain, loss of mobility, and deformity, with resultant adverse consequences on quality of life.[1] The etiology may be multifactorial and may include the disease itself, chemotherapy, poor nutrition, mineral abnormalities, physical inactivity, and ongoing inflammation. The disease process and chemotherapy in combination with several other factors make these complications inevitable. Early recognition of the complications is essential to enable the institution of rational strategies for monitoring and optimizing bone health.

There are few studies performed on Indian children with ALL to assess their bone health, but none evaluating the bone markers.[2,3] The present study was performed to assess alteration in bone mineral metabolism by evaluating the levels of a bone resorptive marker, carboxyl-terminal telopeptide of human type 1 collagen (ICTP), in children with ALL during chemotherapy and to identify risk factors for the altered metabolism.

Materials and Methods

A prospective observational case–control study was performed in the Division of Hematology Oncology, Department of Pediatrics in collaboration with Department of Endocrinology, Institute of Medical Sciences (IMS), Banaras Hindu University (BHU) between November 2015 to May 2017. Newly diagnosed patients with ALL in the age group of 2 to 14 years, without any overt features of rickets or pre-existing renal or liver disease, were included in the study. Relapsed and refractory cases were excluded from the study. Informed written consent was taken from patients/guardians. The study protocol was approved by the ethics committee of IMS, BHU.

All the enrolled children were evaluated and investigated as per protocol. Socio-demographic status, clinic-hematological profile, cytogenetic and immunophenotyping parameters were recorded. The National Cancer Institute criteria were used for risk stratification into standard and high-risk patients based on age, initial white blood cell count, immunophenotyping, central nervous system status, and cytogenetics (when available). They received treatment according to the Children's Oncology Group protocol. Standard risk patients received three drugs (vincristine, L-asparaginase, and dexamethasone) during induction, whereas high-risk patients received four drugs (vincristine, L-asparaginase, dexamethasone, and daunorubicin). High-risk patients also received a BFM (Berlin–Frankfurt–Münster) consolidation and escalating doses of methotrexate (capizzi regimen). Both groups received delayed intensification. None of the patients received cranial irradiation.

Quantitative analysis of bone resorptive marker, ICTP, was assessed at baseline (0 months) and 3 months after chemotherapy by the sandwich enzyme-linked immunosorbent assay technique. The values were documented in each patient profile and were collectively compared with the relevant literature. Thirty age- and gender-matched children were selected as controls. ICTP levels were measured only once in the control population.

Statistical Analysis

Statistical analyses were performed with the trial SPSS for Windows (20.0). Normally distributed data were expressed as means and standard deviations and were compared by Student's *t*-test. The Wilcoxon signed-rank test was used wherever required. Analysis of frequency of difference between B cell and T cell ALL of different categorical variables was done by the chi-square test with continuity correction (Fisher's exact test) when the expected number of cases in any category was <5. The chi-square test was also performed to test association between various patient factors with the ICTP levels.

Results

Fifty patients were enrolled in the study. The mean age was 7.75 ± 4.0 years and the male-to-female ratio was 3.5:1. Baseline characteristics of the study population are presented in ►Table 1. Majority of patients belonged to lower middle class (50%) and were of rural origin (88%). Twenty-seven (54%) patients were underweight as they had body mass index (BMI) <5th percentile. Immunophenotyping was done in 43 patients, where 36 were B cell ALL (83.7%) and 7 were T cell ALL (16.3%). There were 9 females and all belonged to the B cell ALL group, whereas all the 7 patients in T cell group were males. Twenty one (42%) patients belonged to standard risk and 29 (58%) to high risk. Hyperleukocytosis was seen in 16% patients. During the induction phase, 32 patients

Table 1 Baseline characteristics of study population

Variables		Number of patients	Percentage
Age (years)	<6	20	40
	6–9	11	22
	≥10	19	38
Gender	Male	39	78
	Female	11	22
BMI (percentile)	<5	27	54
	≥5	23	46
Risk category	Standard	21	42
	High	29	58
Cell lineage	B cell	36	72
	T cell	7	14
Events	Yes	32	64
	No	18	36

Abbreviation: BMI, body mass index.

Table 2 ICTP levels at 0 and 3 months in study population

Variables		Mean ICTP level ± SD (μg/L)		*p*-Value
		0 month	3 months	
Age (years)	<6	1.77 ± 1.47	3.44 ± 1.46	0.004
	6–9	1.81 ± 1.36	3.40 ± 1.64	0.008
	≥10	1.76 ± 1.40	3.25 ± 1.29	0.020
Gender	Male	1.71 ± 1.29	3.53 ± 1.45	0.001
	Female	2.04 ± 1.77	2.66 ± 0.94	0.214
BMI (percentile)	<5	1.97 ± 1.72	3.61 ± 1.37	0.002
	≥5	1.56 ± 0.88	3.07 ± 1.40	0.001
Risk	Standard	1.79 ±1.63	3.55 ± 1.61	0.002
	High	1.77 ± 1.21	3.20 ± 1.22	0.001
Cell lineage	B cell	1.66 ± 1.30	3.45 ± 1.38	0.001
	T cell	2.04 ± 0.89	2.99 ± 1.18	0.128
Events	Yes	1.72 ± 1.43	3.41 ± 1.30	0.001
	No	1.90 ± 1.81	3.25 ± 1.61	0.011

Abbreviations: BMI, body mass index; ICTP, carboxyl-terminal telopeptide of human type 1 collagen; SD, standard deviation.

suffered from other comorbidities that included both infective and noninfective events. Of the noninfective events, four were tumor lysis syndrome and one case of posterior reversible encephalopathy syndrome. Among infective causes, the most common event was febrile neutropenia followed by culture-positive sepsis, bronchopneumonia, mucosal ulcers, cellulitis, urinary tract infection, and fungal pseudoaneurysm of left common carotid artery.

Serum ICTP levels were analyzed in 44 patients, out of which 37 (84%) showed significantly increased levels. The mean ICTP level in the patients and controls at baseline was 1.78 ± 1.39 and 0.96 ± 0.32 μg/L ($p = 0.001$), respectively. The mean ICTP levels in patients increased significantly at 3 months compared with baseline (1.78 ± 1.39 vs. 3.55 ± 1.40 μg/L, $p = 0.001$). The level was already raised in majority of the patients at the diagnosis, which further increased after chemotherapy, suggesting that the disease itself caused bone resorption.

Patient characteristics were compared with the raised ICTP levels at both time points of 0 and 3 months (►**Table 2**). The levels were significantly increased in males ($p = 0.000$) and in the B cell ALL group ($p = 0.000$) in comparison to females and the T cell group. Both high and standard risk groups were equally affected ($p = 0.000$). It was also significantly increased in both the groups based on BMI and occurrence of events during hospital stay. However, on multivariate analysis no single risk factor could be found.

Discussion

Bone morbidity is a significant complication of treatment of ALL. The leukemic process itself has an adverse effect on bone mineral metabolism. There are several studies which have looked at skeletal morbidity in patients and survivors of childhood ALL. Majority of these have focused on bone mineral density as a marker of bone metabolism.[4,5] However, there are several biochemical markers that may shed light on the dynamic process of bone turnover and growth. C-terminal propeptide of type I collagen (PICP), marker of bone formation, N-terminal propeptide of type III collagen, marker of soft tissue turnover, and ICTP, marker of bone resorption are some of them.[6] In our study, ICTP was used to evaluate the alteration in bone mineral metabolism in newly diagnosed patients with ALL.

Our results show that even at diagnosis the ICTP levels were higher than normal, which suggests that the disease itself adversely affects bone metabolism before any therapy is started. When the mean ICTP levels at 3 months were compared with baseline levels, the values were significantly higher. Similar results were observed in other studies also where PICP and ICTP levels were assessed at baseline and after chemotherapy. PICP levels were significantly decreased at diagnosis, which normalized at the end of follow-up. But the marker of bone resorption, ICTP, was significantly increased after 1 year.[7-9] This suggests a role of chemotherapy and the disease process in bone resorption. ICTP is largely cleared by the kidneys.[10] Thus the elevated serum levels could be partly due to impaired renal function. However, we observed no increase in the level of serum creatinine during the study period.

Some of the studies have reported that both formative and resorptive markers were reduced at diagnosis, which indicates suppressed bone mineralization.[9,11,12] Bone metabolism was evaluated in children and adolescents with newly diagnosed ALL by assessing biomarkers of bone cell activity. More significant disturbances in bone turnover, particularly in bone formation (suppression of collagen synthesis), were observed in children with untreated ALL in comparison with adolescents with ALL, suggesting the role of age of onset of ALL on bone metabolism.[11] In our study, we aimed to derive a correlation between the bone mineral metabolism and various factors like age, gender, nutritional status,

risk stratification, cell lineage, and other associated comorbidities that occurred during induction chemotherapy as T cell lineage was found to be associated with higher ICTP levels compared with B cell lineage.[13,14] When the levels of ICTP were compared in different age groups, they were increased significantly in all these age groups after 3 months (p-value < 0.05). However, we could not derive a significant correlation between age and ICTP levels. Similarly, no significant correlation could be found between other factors and raised ICTP levels.

The strength of our study is that we have evaluated the levels of one of the biomarkers of bone metabolism (ICTP) in Indian children for the first time. The limitations of this study are the small number of participants and lack of bone mineral density data.

Funding
None.

Conflict of Interest
Authors have no conflict of interest.

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