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RESEARCH BRIEF

Incidence and Risk Factors For Hypertension During Childhood Acute Lymphoblastic Leukemia Therapy

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ABSTRACT

Objective: To determine the incidence of hypertension among children during the induction and re-induction phases of acute lymphoblastic leukemia (ALL) therapy and association with possible risk factors.

Methods: A retrospective analysis of 208 consecutive pediatric (age <18 y) ALL patients, treated per BFM-95 protocol from January 2009 and December 2013. Demographics, disease, treatment and toxicity data were abstracted from medical records and were analyzed to determine the incidence of hypertension and risk factors for its development.

Results: Incidence of hypertension requiring antihypertensive medication, was 29% (61/208) during induction and 17% (33/198) during re-induction (P=0.003). Median (range) age of patients developing hypertension was 4 years (4 months to 8 years). Age <10 years and presence of constipation were independently predictive of hypertension by both univariate and multivariate analysis.

Conclusion: The present study reports a high incidence of hypertension among children undergoing ALL induction therapy and its strong association with young age and constipation.

Keywords: *Blood pressure, Childhood cancers, Complications, Treatment*.

Acute lymphoblastic leukemia (ALL) is the commonest childhood malignancy and has excellent cure rates with contemporary treatment strategies [1,2]. Glucocorticoids form the backbone of induction and re-induction phases of ALL therapy and hypertension (HT) is an important though often under-reported non-hematological toxicity associated with its use [3-9]. There are no reports from India and the risk factors for developing HT are not well understood. Hence, this study was undertaken to determine the incidence of HT and its association with possible risk factors among children receiving treatment for ALL.

METHODS

This was a retrospective study of 208 newly diagnosed ALL patients <18 years of age, diagnosed between January 2009 and December 2013, in the pediatric hematology oncology department of a tertiary care cancer centre in Northern India. Exclusion criteria included previously treated patients or those with relapse, pre-existing kidney disease or HT. All patients received a 4-drug induction with prednisolone, vincristine, daunorubicin and L-aparaginase (BFM-95 protocol) [10]. The study was approved by the Institutional Ethics Committee.

Data regarding HT were retrieved from the electronic medical records by individually reviewing all inpatient and outpatient notes and discharge summaries for documented blood

pressure (BP) readings, use of antihypertensive medications and mention of HT. Patient demographics, disease and treatment details and induction/re-induction toxicities such as HT, hyperglycemia, constipation, thrombosis, hepatopathy, neuropathy, nephropathy, febrile neutropenia and mucositis were noted and graded by Common Terminology Criteria for Adverse Events (CTCAE 4.03) criteria [11]. All toxicities including HT were followed till their resolution.

For the purpose of this study HT was defined as an average daily systolic or diastolic BP value ≥95th percentile for the subject's age, gender, and height. A minimum of 3 readings per day was used to calculate the average daily BP [12]. Anti-hypertensive medication were prescribed for patients with stage II HT, persistent stage I HT (≥3 days) or complicated HT. Constipation was considered to be present if it was persistent despite regular use of laxatives or enema (CTCAE grade 2) or more severe.

Statistical analysis: Statistical summaries were presented as median and inter quartile range (IQR) and clinical data were compared by chi square test. Risk factors were analyzed by univariate and stepwise multivariate logistic regression analysis. *P* value <0.05 was considered to be statistically significant. Data was analysed using SPSS version 20.0., 2011, Chicago, USA.

RESULTS

The data of 208 eligible patients were analyzed. The median age was 6 years (0.5-18 years), 76% were male, 80% had B immunophenotype and 56% had moderate risk disease. Incidence of HT was 29% (61/208). Except for age and constipation, all clinical characteristics and incidence of induction toxicities were comparable among the hypertensive and non-hypertensive patients (***Table* I**). Constipation was observed to be in 46% (28/61) hypertensive and 13.6% (20/147) non-hypertensive children (*P* value <0.0001). Most patients (54/61) with HT were asymptomatic. Headache not attributable to other causes was observed in 10% (6/61), and one patient had posterior reversible encephalopathy (PRES). The median time to HT detection was day 10 of induction (range, 3-25 days). All 61 patients received at least one antihypertensive medication (amlodipine) while 11 children required two or more drugs (labetalol, enalapril). Among the hypertensive patients, 51/61 became normotensive within one week of cessation of prednisolone therapy (by day 40) and the rest by day 140. Glucocorticoid therapy was continued in all patients regardless of severity of HT.

On univariate and multivariate analysis the age at diagnosis (*P*=0.011; *P*=0.006) and presence of constipation (*P*=<0.0001; <0.0001) were independently predictive of HT. Children ≤10 years had 2.9 times increased odds of developing HT as compared to older children. Logistic regression analysis revealed that with each one year increase in age, the risk of HT decreased by 9%, excluding infants ≤12 months of age (*P*=0.008). It was further

observed that the odds of developing HT, was 5.9 times higher among patients with constipation.

During re-induction the incidence of HT and constipation were significantly lower than induction (17% *versus* 29%, *P*<0.001 and 14% *versus* 30%, *P*=0.04), respectively. HT was observed among 12/33 patients for the first time during re-induction.

DISCUSSION

In this retrospective analysis we report a high incidence (29%) of glucocorticoid induced HT requiring antihypertensive medication in children on ALL induction. This is in accordance with published literature (13-67%) from across the globe [3-9]. Differences in ethnicity, definition of HT, nutrition status, dose of steroids and anti-leukemic therapy are the likely reasons contributing to this diversity [3-9]. This is the first report from India and the largest so far from Asia and the Middle-East [8-9].

While HT is a known adverse effect of the mineralocorticoid effect of steroids, leukemic infiltration of kidney, impact of large sodium and fluid volumes as well as influence of anemia, pain, and stress have also been implicated as contributory factors in induction [4-7,13]. Resolution of these factors and use of dexamethasone which has relatively lesser mineralocorticoid potency may explain lower incidence of HT during re-induction [14].

Two important risk factors for development of steroid induced HT were age less than 10 years and constipation (grade ≥2) which have not been previously reported. Differences in prednisolone clearance and sensitivity of hypothalamic-pituitary axis have been postulated as possible mechanism for increased incidence of HT in young children [3-7]. Constipation is one of the established adverse effects of vincristine related autonomic neuropathy and often leads to abdominal pain and straining. Influence of constipation on the incidence and severity of HT needs prospective evaluation.

The main limitation of this study is the retrospective design possibly lending to underestimation of the incidence of HT.

Anticipation and appropriate management of both HT and constipation are simple measures that may avoid serious, though rare, complications and end-organ damage in a curable condition like ALL. Knowledge of the pattern and trend of HT among pediatricians would help guide monitoring strategies and prevent treatment interruptions. The authors suggest that regular blood pressure measurement should be an important part of the physical examination of a child undergoing induction/re-induction phases of ALL therapy.

Contributors: PM: retrieved, compiled and analysed the data and drafted the manuscript; GK: study concept and design, supervision of data analysis, critical revision and finalisation of manuscript; SJ: Helped in data analysis and revision of manuscript; BG: statistical analysis and interpretation of data. All authors approved the final manuscript.

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WHAT THIS STUDY ADDS?

- A high incidence of hypertension (29%) was observed in Indian children undergoing ALL induction therapy.
- Age <10years and constipation were independent risk factors for development of hypertension.

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TABLE I DEMOGRAPHICS, DISEASE AND TOXICITY DATAOF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIADURING INDUCTION THERAPY

Characteristic	*HT present N*= 61	*HT absent N*=147	*P value*
Age (y)*	4 (3-8)	6 (3-12)	0.006
Age >10 y	12 (17.7)	56 (82.3)	0.008
Male gender	44 (27.7)	115 (72.3)	0.346
BMI *Z*-score <-2	32 (30.8)	72 (69.2)	0.70
Initial TLC (>$10^5/\mu$L)	14 (31.8)	30 (68.2)	0.683
Deranged KFT	20 (35.0)	37 (65.0)	0.263
Immunophenotype			
B immunophenotype	48 (29.0)	118 (71.0)	
T immunophenotype	13 (31.7)	28 (68.3)	0.763
Biphenotype	0 (0.0)	1 (100.0)	
High	14 (28.6)	35 (71.4)	
Moderate	32 (27.3)	85 (72.7)	0.588
Standard	15 (35.0)	27 (65.0)	
Toxicity			
Hyperglycemia (grade ≥2)	6 (35)	11 (65)	0.573
Hepatopathy (grade ≥2)	3 (33)	6 (67)	0.724
Constipation (grade ≥2)	28 (58)	20 (42)	<0.0001
Thrombosis (CSVT)	0 (0.0)	4 (100.0)	0.557
Mucositis (grade ≥2)	1 (25)	3 (75)	1.0
FN requiring hospitalization	16 (22)	56 (78)	0.102
Induction mortality	0	2 (100)	0.9

HT: *Hypertension; BMI*: *Body mass index; TLC: total leukocyte count; KFT: kidney function test (deranged defined as >1.5 times upper limit of normal). FN: febrile neutropenia, CSVT: cerebral sino-venous thrombosis.*

*Value in Number (%) except * median (IQR)*

TABLE II UNIVARIATE AND MULTIVARIATE ANALYSIS OFPREDISPOSING RISK FACTORS FOR HYPERTENSION DURINGINDUCTION THERAPY

Characteristic	*Odds ratio (95% CI)*
Age>10 y	0.40 (0.20, 0.81)
	0.34 (0.16, 0.74)*
Male gender	0.72 (0.36, 1.43)
BMI *Z*-score <-2 to 2	0.89 (0.49, 1.62)
BMI *Z*-score >2	0.56 (0.06, 5.2)
Hyperleukocytosis	1.16 (0.56, 2.3)
Deranged KFT	1.45 (0.75, 2.78)
T Immunophenotype	1.16 (0.55, 2.42)
Biphenotypic	0.81 (0.01, 76.2)
Moderate BFM Risk	0.94 (0.5, 1.97)
Standard BFM Risk	1.39 (0.57, 3.36)
Febrile neutropenia	0.58 (0.30, 1.12)
Mucositis (grade ≥2)	2.46 (0.34, 17.8)
Hyperglycemia (grade ≥2)	0.72 (0.23, 2.31)
Hepatopathy (grade ≥2)	1.22 (0.29, 5.02)
Constipation (grade ≥2)	5.39 (2.70, 10.7)
	5.93 (2.89, 12.10)*

KFT: *Kidney function test (deranged defined as >1.5 times upper limit of normal),* BMI: Body *mass index, Hyperleucocytosis; WBC >1x10^5/μL.*

**By multivariate analysis*