RESEARCH PAPER

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

PAYAL MALHOTRA, GAURI KAPOOR, SANDEEP JAIN AND BHAWNA GARG
From Department of Pediatric Hematology Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India.

Correspondence to: Dr Gauri Kapoor, Director, Department of Pediatric Hematology Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Rohini sector 5, Delhi 110 085, India. kapoor.gauri@gmail.com
Received: October 23, 2017; Initial Review: March 18, 2018; Accepted: May 23, 2018.

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 between January 2009 and December 2013. Data 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 y (4 mo to 8 y). Age <10 y and presence of constipation were independently predictive of hypertension by multivariate analysis. **Conclusion:** The present study reports a high incidence of hypertension among children undergoing ALL induction therapy.

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

Published online: July 13, 2018. PII:S097475591600125

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 is an important though often under-reported non-hematological toxicity associated with its use [3-9]. There are no reports from India on the risk factors for developing hypertension are not well understood. Hence, this study was undertaken to determine the incidence of hypertension 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 center. Exclusion criteria included previously treated patients or those with relapse, pre-existing kidney disease or hypertension. 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 hypertension were retrieved from the electronic medical records by individually reviewing all inpatient and outpatient notes and discharge summaries for documented blood pressure readings, use of antihypertensive medications and mention of hypertension. Patient demographics, disease and treatment details and induction/re-induction toxicities such as hypertension, 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].

Hypertension was defined as an average daily systolic or diastolic blood pressure 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 blood pressure [12]. Constipation was considered to be present if it was persistent despite regular use of laxatives or enema (CTCAE grade 2) or more severe.

Statistical analyses: 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.

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 hypertension was 29%. 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 <0.0001). Most patients (54) with hypertension were asymptomatic; headache not attributable to other causes was observed in 10% (6), and one patient had posterior reversible encephalopathy (PRES). The median time to hypertension 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 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 hypertension.

On multivariate analysis, the age at diagnosis (P=0.006) and presence of constipation (P<0.0001) were independently predictive of hypertension. 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% *vs* 29%, P<0.001 and 14% *vs* 30%, P=0.04, respectively). Hypertension was observed among 12/33 patients for the first time during re-induction.

TABLE I CHARACTERSTICS OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA DURING INDUCTION THERAPY

Characteristic	*HT present* n= 61	*HT absent* n=147	*P value*
Age (y)*	4 (3-8)	6 (3-12)	<0.01
Age >10 y	12 (17.7)	56 (82.3)	<0.01
Male gender	44 (27.7)	115 (72.3)	0.35
BMI *Z*-score <-2	32 (30.8)	72 (69.2)	0.70
Initial TLC (>10^5/5/μL)	14 (31.8)	30 (68.2)	0.68
Deranged KFT	20 (35.0)	37 (65.0)	0.26
Immunophenotype			
B immunophenotype	48 (29.0)	118 (71.0)	
T immunophenotype	13 (31.7)	28 (68.3)	0.76
Biphenotype	0 (0.0)	1 (100.0)	
Risk			
High	14 (28.6)	35 (71.4)	
Moderate	32 (27.3)	85 (72.7)	0.59
Standard	15 (35.0)	27 (65.0)	
Toxicity			
Hyperglycemia (grade ≥2)	6 (35)	11 (65)	0.57
Hepatopathy (grade ≥2)	3 (33)	6 (67)	0.72
Constipation (grade ≥2)	28 (58)	20 (42)	<0.001
Thrombosis (CSVT)	0 (0.0)	4 (100.0)	0.56
Mucositis (grade ≥2)	1 (25)	3 (75)	1.0
FN requiring hospitalization	16 (22)	56 (78)	0.1
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; Values in number (%) except *median (IQR).*

DISCUSSION

In this retrospective analysis we report a high incidence (29%) of glucocorticoid-induced hypertension 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 hypertension, nutrition status, dose of steroids and anti-leukemic therapy are the likely reasons contributing to this diversity [3-9].

While hypertension 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

TABLE II RISK FACTORS FOR HYPERTENSION DURING INDUCTION 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 >1×10^5/5/μL; *By multivariate analysis.*

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.

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 hypertension during re-induction [14].

Two important risk factors for development of steroid-induced hypertension 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 hypertension 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 hypertension needs prospective evaluation.

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

Anticipation and appropriate management of both hypertension and constipation are simple measures that may avoid serious, though rare, complications and end-organ damage in a curable condition like ALL. We 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.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Riehm H, Feickert HJ, Schrappe M, Henze G, Schellong G. Therapy results in five ALL-BFM studies since 1970: Implications of risk factors for prognosis. Haematol Blood Transfus. 1987;30:139-46.
2. Arora RS, Arora B. Acute leukemia in children: A review of the current Indian data. South Asian J Cancer. 2016;5: 155-60.
3. Kamdem LK, Hamilton L, Cheng C, Liu W, Yang W, Julie A, *et al.* Genetic predictors of glucocorticoid-induced hypertension in children with acute lymphoblastic leukemia. Pharmacogenet Genomics. 2008;18:507-14.
4. Louis CU, Butani L. High blood pressure and hypertension in children with newly diagnosed acute leukemia and lymphoma. Pediatr Nephrol. 2008;23:603-9.
5. Attard-Montalto SP, Saha V, Ng YY, Kingston JE, Eden OB. High incidence of hypertension in children presenting with acute lymphoblastic leukemia. Pediatr Hematol Oncol.1994;11:519-25.
6. Bakk I, O'Brien S, Reed S, Koch T. Steroid-induced hypertension during induction chemotherapy for acute lymphoblastic leukemia in US children's hospitals. Blood. 2014;124:3651.
7. Bakk I, Koch T, Stanek J, O'Brien SH, Reed S. Steroid-induced hypertension during induction chemotherapy for acute lymphoblastic leukemia in us children's hospitals. J Pediatr Hematol Oncol. 2018;40:27-30.
8. Juliansen A, Andriastuti M, Sudung OP, Sekartini R. Hypertension, high-dose corticosteroids, and renal infiltration in children with acute lymphoblastic leukemia. Paediatrica Indonesiana. 2014;54:324-9.
9. Belgaumi AF, Al-Bakrah M, Al-Mahr M, Al-Jefri A, Al-Musa A, Saleh M, *et al*. Dexamethasone-associated toxicity during induction chemotherapy for childhood acute lymphoblastic leukemia is augmented by concurrent use of daunomycin. Cancer. 2003;97:2898-903.
10. Möricke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dördelmann M, *et al.* Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: Treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood. 2008;111:4477-89.
11. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03: U.S. department of health and human services National Institutes of Health National Cancer Institute. 2009 (v4.03: 2010).
12. Bagga A, Jain R, Vijayakumar M, Kanitkar M, Ali U. Evaluation and management of hypertension. Indian Pediatr. 2007;44:103-21.
13. Olgar S, Yetgin S, Cetin M, Aras T. Can renal leukemic infiltration cause hypertension in children. J Pediatr Hematol Oncol. 2006;28:579-84.
14. Hill MR, Szefler SJ, Ball BD, Bartoszek M, Brenner AM. Monitoring glucocorticoid therapy: A pharmacokinetic approach. Clin Pharmacol Ther. 1990;48:390-8.