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Original Research Article

Evaluation of hematological and biochemical factors of hypertension during the induction chemotherapy for childhood acute lymphoblastic leukemia

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is a prevalent childhood cancer, accounting for approximately 25% of all pediatric cancer cases. The incidence of hypertension in ALL patients is significantly higher compared to the general pediatric population, emphasizing the need for a better understanding and management of this condition. The aim of the study was to evaluate hematological and biochemical factors of hypertension during the induction of chemotherapy for childhood ALL.
Methods: This prospective observational study was conducted in the Department of Pediatric Hematology and Oncology at BSMMU from July 2017 to June 2018. The study included 93 newly diagnosed cases of ALL in children aged 1 to 17.9 years, excluding those below 1 year and above 18 years, known cases of hypertension, patients with pre-existing hypertension before chemotherapy, and old or relapse cases of ALL.
Results: The study found that 17.2% of the study population experienced renal derangement during the induction remission phase, while the majority (82.8%) did not. The presence of renal derangement was not significantly associated with hypertension. However, patients who developed tumor lysis syndrome (TLS) had a higher percentage (12.5%) of hypertension compared to the non-hypertensive group (1.3%). Febrile neutropenia, convulsion, and coagulopathy were also observed in patients who developed hypertension more frequently. The median time to detect hypertension during induction chemotherapy was on day 8, with a mean duration of 13.6 days.
Conclusions: In this study, hypertension is observed in 17.2% of patients during induction chemotherapy for ALL with higher frequency in the second week and associations with tumor lysis syndrome, febrile neutropenia, convulsion, and coagulopathy.

Keywords: Acute lymphoblastic leukemia, Hypertension, Induction chemotherapy, Hematological and biochemical

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most prevalent form of cancer in children and is highly treatable with modern treatment approaches.[1,2] In Bangladesh, there is a lack of research on the risk factors contributing to the development of hypertension in ALL patients. Therefore, this study was conducted to

determine the frequency of hypertension and its potential correlation with various risk factors among children undergoing treatment for ALL. ALL is a prevalent form of cancer among children, accounting for approximately 25% of all cancer cases in this age group. It primarily affects the blood and bone marrow, which is the soft tissue found inside the bones. In the case of ALL, an excessive number of stem cells in the bone marrow undergo abnormal development, resulting in the proliferation of specific types of abnormal blood cells. At the Department of Paediatric Hematology and Oncology in BSMMU, a study conducted by Islam et al reported that among 455 newly diagnosed children with malignancy, 58% of cases were identified as ALL within a one-year period.[3] Over time, the 5-year survival rate for children with ALL has significantly improved and currently exceeds 85% (Cancer Statistics 2017).

To treat these patients, chemotherapy and stem cell transplantation (HSCT) have emerged as established therapeutic options. The presence of hypertension before therapy and its association with renal enlargement suggests that the leukemic process is an important etiologic factor.[4] The admission of patients with renal dysfunction or acute kidney injury is uncommon and the presentation of patients with leukemic infiltration of the kidney is usually silent. It also causes renal failure, hypertension, or asymptomatic kidney enlargement. Several factors cause impairment of renal function in children with leukemia, infiltration of kidneys by leukemic cells, nephrotoxicity and metabolic change arising from chemotherapy, radiotherapy, infection, treatment with nephrotoxic antibiotics and intravascular coagulopathy may cause renal damage.[5] Volume depletion from poor oral fluid intake, anorexia, early satiety, emesis, and diarrhea contribute to prerenal AKI.

Obstruction from direct compression or encasement of ureteral outflow by tumor or lymph nodes, retroperitoneal fibrosis, or nephrolithiasis from tumor lysis syndrome may contribute post renal AKI. Intrarenal causes of kidney injury in hematologic malignancy can be from severe volume depletion, heart failure, sepsis and drug-induced injury.[6] Retrospectively, reviewed the diagnosis, age at presentation, race, gender, body mass index, admission hematologic and chemistry laboratory values, diagnosis of tumor lysis syndrome, daily BP measurement and the use of antihypertensive medications with the aim to detect the prevalence and predictors of HBP and HTN in newly diagnosed acute leukemia and lymphoma patients among 102 children at the University of California, Davis Children's Hospital, from January 1, 1997 to July 30, 20037. They found 68.6% and 52.9% were identified as HBP and HTN prior to chemotherapy, and 78.4% and 67.3% post chemotherapy respectively.

The mean time to blood pressure normalization was 54 days. Only 15% of patients received antihypertensive therapy. There a significant association between was prechemotherapy HBP and younger age at diagnosis (p=0.025) and lower eGFR (p=0.003) and a trend was seen with lower admission total white blood cell count (p=0.056). For post chemotherapy HBP, an association with younger age at diagnosis (p=0.004) was seen. Post chemotherapy HBP and HTN were both associated with eGFR. For every 10% increase above normal in the eGFR, the odds of developing post chemotherapy HBP and HTN decreased by 16.3% (p=0.014) and 14.3% (p=0.032) respectively.

According to the findings of various studies around the world, it is clear that the incidence of hypertension is higher in ALL patients than the general population and it is 10 times higher than the general pediatric population. 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.[8-13] No study has been conducted on pediatric population in Bangladesh. Through the study, we shall come to know about the incidence and risk factors of hypertension in childhood acute lymphoblastic leukemia which would give more insight into the spectrum of problem and would help to design follow-up plans and in planning treatment in our population. Therefore, hypertension-related morbidity will reduce in children with ALL in the long term.

Objectives

General

The general objectives was to evaluate the hematological and biochemical factors of hypertension during the induction chemotherapy for childhood ALL.

Specific

The specific objectives were to detect the incidence of hypertension during induction chemotherapy in childhood ALL; and to explore the risk factors associated with hypertension during induction chemotherapy in childhood ALL.

METHODS

The prospective observational study was conducted in the Department of Pediatric Hematology and Oncology, BSMMU for the period of one year July 2017 to June 2018. All newly diagnosed cases of ALL between 1 to 17.9 years of age were admitted into the Department of Pediatric Hematology and Oncology. BSMMU, Dhaka for treatment during the study period. Aged 1 to 17.9 years, diagnosed cases of ALL, admitted cases, and normotensive at diagnosis were included in the study. Age less than 1 year, age 18 years or more, known case of hypertension, hypertension before starting chemotherapy, and old or relapse case of ALL were excluded from the study.

Sample size

It was calculated using the following formula,

calculated sample size=n-pa[16],

n=total number of the sample,

P=sample proportion or expected proportion of event (prevalence or proportion of occurrence). In this study, 'p' considered as % of incidence or prevalence. The exact incidence of hypertension during induction chemotherapy among pediatric ALL in Bangladesh is not known; but in a few studies that were done earlier in abroad, it was around 10%15. So, it was regarded as p=0.1 (10%). Here, P=prevalence (10%)=0.1,

q-1-p-1-0.1-0.9,

z=confidence interval=1.96 for 95% confidence level,

e=accepted standard error=0.05, calculated sample size was n=2pq,

=(1.96)×0.1×0.9/(0.05)

=138.

So, the sample size would be 138. Due to time limitations and facilities constraints, a total of 120 samples were taken.

This study involved a COHORT of 120 children diagnosed with ALL. Out of this group, 19 patients unfortunately passed away, and an additional 8 patients chose to discontinue treatment against medical advice. As a result, the data analysis focused on the remaining 93 patients.

Hematological and biochemical parameters: WBC count at diagnosis, hyperleucocytosis type of ALL, CNS involvement at diagnosis, Initial eGFR status, initial uric acid level, renal derangement.

Data analysis

The data analysis process consisted of the following steps: manual collection and editing of data, verification and checking of entered data, and analysis using appropriate computer software. The results were presented in tabular or diagrammatical form. A systematic record was maintained using a preformed data collection form. Statistical analysis was conducted using SPSS for Windows version 22.0. A significance level of $p<0.05$ and a confidence interval of 95% were considered statistically significant. The odds ratio for developing hypertension was calculated for each variable. Univariate analysis using the chi-square test was performed for selected risk factors, and multivariate logistic regression analysis was conducted to control for confounding factors.

RESULTS

This prospective observational study was conducted at a single center, the Department of Pediatric Hematology and Oncology at Bangabandhu Sheikh Mujib Medical University, over a one-year period from July 2017 to July 2018. The study population comprised newly diagnosed ALL patients of both sexes aged 1 to 17.9 years, who were admitted to the Department of Pediatric Hematology and Oncology. A total of 120 children diagnosed with ALL were initially enrolled in this study. Unfortunately, 19 patients succumbed to their condition, and an additional 8 patients opted to discontinue treatment against medical advice. Consequently, the final data analysis was carried out on the remaining 93 patients.

Table 1 shows initial characteristics of study population. In this study, most of the patients were in the age group of <10 years 76 (81.7%), remaining were in the age group of ≥10 years. Mean age was 6.0±3.78 years, median age was 4.5 years and range were between 1.30 to 15.0 years. Among 93 patients, 59 (63.4%) were male and 34 (36.6%) were female patients. Male children were predominant in number. Male:female ratio was 1.7:1. On BMI category of study subjects, among 86 patients 43 (50.0%) were normal, 36 (41.8%) were underweight, 6 (7.0%) were overweight and 1 (1.2%) was obese. Only 8 (8.6%) patients had a positive family history of hypertension. 52 (55.9%) were treated with regimen A, whereas 41(44.19%) were treated with regimen B. Age under 2 years was not included in BMI calculation. There were 7 patients below 2 years of age. So, the number of patients was 86 while calculating BMI.

Table 1: Initial characteristics of the study patients (n=93).

Characteristics		Frequency	Percentage (%)
Sex	Male	59	63.4
	Female	34	36.6
Age (in years)	<10	76	81.7
	≥10	17	18.7
BMI category	5th. 85th percentile	43	50.0
	<5th percentile	36	41.8
	85th-95th percentile	6	7.0

Continued.

Characteristics		Frequency	Percentage (%)
	>95th percentile	1	1.2
Family history of HTN	Yes	8	8.6
	No	85	91.4
Treatment regimen	A	52	55.9
	B	41	44.1

Table 2: Hematological and biochemical parameters of the study patients (n=93).

Characteristics		Frequency	Percentage (%)
Initial WBC count (per cumm.)	<50,000	63	67.7
	≥ 50,000	30	32.3
	Total	93	100.0
Type of ALL	B-cell lineage	85	92.4
	T-cell lineage	7	7.6
	Total	92*	100.0
CNS status	CNS1	90	96.8
	CNS2	2	2.2
	CNS3	1	1.1
	Total	93	100
Initial Egfr status (ml/min/1.73m²)	> 125	15	16.1
	90-124	12	12.9
	60-89	53	57.0
	30.59	13	14.0
	Total	93	100
Higher initial uric acid level	Present	8	8.6
	Absent	85	91.4
	Total	93	100.0

Table 3: Renal derangement of study subjects during induction remission (n=93).

Renal derangement	Frequency	Percentage (%)
Yes	16	17.2
No	77	82.8
Total	93	100.0

Table 4: Measurement of risk factors for hypertension in children of ALL with some hematological and biochemical parameters (n=93).

Factors	Patients with hypertension (n=16)	Patients without hypertension (n=93)	OR CI 95%	P value
	N (%)	N (%)		
Initial WBC count (per cumm)				
<50000	10 (62.5)	53 (68.8)	0.755	0.622^{ns}
≥50000	6 (37.5)	24 (31.2)	(0.25-2.31)	
Hyperleucocytosis				
<1,00,000	12 (75.0)	61 (79.2)	0.787	0.708^{ns}
≥1,00,000	4 (25.0)	16 (20.8)	(0.22-2.77)	
Type of ALL*				
B cell lineage	14 (93.3)	71 (92.2)	1.18	0.880^{ns}
T cell lineage	1 (6.7)	6 (7.8)	(0.13-10.61)	
CNS involvement at diagnosis				
Yes	2 (12.5)	2 (2.6)	5.36	0.076^{ns}
No	14 (87.5)	75 (97.4)	(0.69-41.2)	
TLS				

Continued.

Factors	Patients with hypertension (n=16)	Patients without hypertension (n=93)	OR CI 95%	P value
Yes	2 (12.5)	1 (1.3)	10.857	0.021
No	14 (87.5)	76 (98.7)	(0.92-128.0)	
eGFR at diagnosis				
>125	5 (31.3)	10 (13.0)	3.05	0.071^{ns}
<125	11 (68.7)	67 (87.0)	(0.87-16.62)	
Initial uric acid level				
Increased	2 (12.5%)	6 (7.8)	1.690	0.541^{ns}
Normal	14 (87.5)	71 (92.2)	(0.31-9.25)	
Renal derangement				
Yes	1 (6.3)	15 (19.5)	0.276	0.202^{ns}
No	15 (93.8)	62 (80.5)	(0.03-2.25)	

Table 5: Induction toxicities of children with ALL (n=93).

Toxicity	Patients with hypertension (n=16)	Patients without hypertension (n=77)	P value
	N (%)	N (%)	
Febrile neutropenia	10 (62.5)	20 (26.0)	0.004
Diarrhea	2 (12.5)	2 (2.6)	0.076^{ns}
Coagulopathy	3 (18.8)	3 (3.9)	0.028
Convulsion	2 (12.5)	0 (0.0)	0.002
Septic shock	0 (0.0)	1 (1.3)	0.647^{ns}
Hyperglycemia	1 (6.3)	1 (1.3)	0.214^{ns}

Table 6: Outcome of hypertension at the end of induction (n=16).

Outcome	Frequency	Percentage (%)
Improved	12	75.0
Persistence	4	25.0
Total	16	100.0

Table 7: Hypertensive patient's characteristics, time required to normalization of hypertension (n=16).

S. No	ID No	Age (yrs)	Sex	Development of HTN at Day of induction	Resolution of HTN at Day of induction	Time required to normalization
1.	1	7	Male	17	Not	persisted
2.	3	8	Female	13	Resolved28	15
3	16	3	Male	8	Not resolved	Persisted
4	28	4	Male	7	12	6
5.	31	13	Female	7	28	22
6.	33	15	Male	14	Not resolved	Persisted
7.	36	3	Female	4	16	13
8.	45	4	Male	14	17	4
9.	62	2.6	Male	1	15	15
10.	67	14	Male	9	21	13
11.	74	3	Male	5	13	9
12.	78	4	Male	21	Not resolved	Persisted
13.	97	7	Female	25	30	6
14.	110	4	Female	2	16	15
15.	112	3	Male	3	9	7
16.	115	7	Male	4	12	9

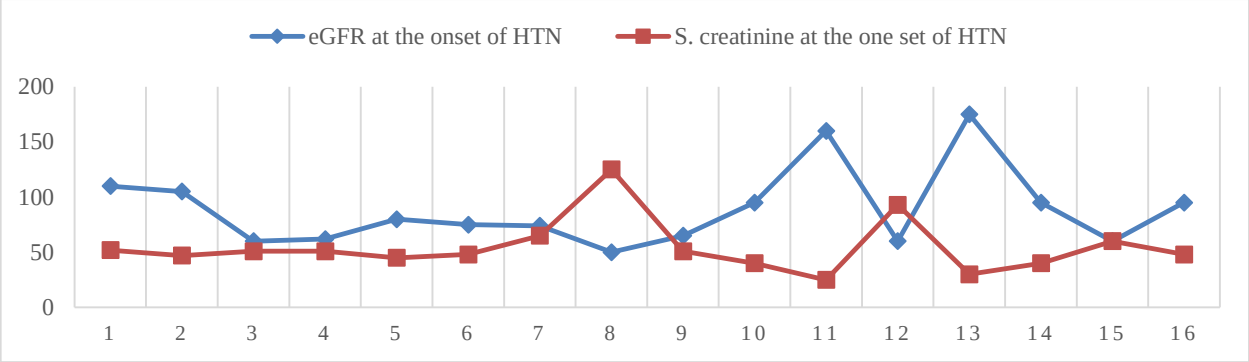

Figure 1: Graphical representation of eGFR and S. creatinine level of hypertensive patients.

Table 2 summarizes the patient characteristics at diagnosis. Among the patients, 63 (67.7%) had a WBC count <50,000 /cumm, while 30 (32.3%) had a WBC count ≥250,000 /cumm. The majority of patients, 85 (92.4%), had B cell lineage ALL, while 7 (7.6%) had T cell lineage ALL. No patients had mixed cell lineage ALL. CNS status, determined through CSF analysis, revealed that 90 (96.8%) patients were classified as CNS 1, 2 (2.2%) as CNS 2, and only 1 (1.1%) as CNS 3. At diagnosis, 8 (8.6%) patients had hyperuricemia, while 85 (91.4%) patients had a normal initial uric acid level.

Table 3 shows the renal derangement of study subjects during induction remission, 17.2% had renal derangement, while 82.8% had no renal derangement during the period of induction remission.

Table 4 shows patients who developed TLS had higher percentage (12.5%) of hypertension than the non-hypertensive group (1.3%), OR10 857 (95% CI 0.92-128.0), p=0.021), 68.7% patient had 125 ml/min/1.73 m eGFR at diagnosis IM hypertensive group, patients with B cell lineage ALL had higher percentage (93.3%) of hypertension.

Figure 1 shows relation of eGFR status with serum creatinine level at the onset of hyperion. Serum creatinine level was within normal limit in spite of eGFR status ept one patient who had GBS followed by AKI.

Table 5 shows toxicity of children with ALL, among 93 patients febrile neutropenia was observed in 62.5% patients (p=-0 004), convulsion was observed in 12.5% patients (p=0.002), coagulopathy was observed in 18.8% patients (p=0.028) indicating patients having febrile neutropenia, convulsion or coagulopathy developed hypertension more. Other toxicities like septic shock, hyperglycemia, and diarrhea during induction period were not statistically significant.

Table 6 shows the outcome of hypertension among the study population at the end of induction. Among total of 93 patient's hypertension was observed in 16 cases. 12 (75%) patients became normotensive after certain period during induction remission and hypertension persists at the end of induction remission in 4 (25%) patients.

Table 7 shows a total of 16 patients' characteristics, development, and outcome hypertension during induction chemotherapy, the median time to detect hypertension was day 8 of induction (range, 1-25), mean time to duration hypertension was 13.6 days.

DISCUSSION

Hypertension is one of the common complications during induction therapy, and when associated with other complications leads to serious morbidity and treatment interruption, which may contribute to relapse in the future.[14] Supported this hypothesis, they found most of the patients become normotensive within 2 months after the initiation of chemotherapy (mean time to BP normalization 54 days).[7] In this study, there was a male predominance with a male-female ratio of 1.7:1 sex, family history of hypertension, BMI category and CNS status cannot be considered as risk factors in this study, because those factors had no statistically significant relation with having hypertension.

It was believed that hyperuricemia in tumor lysis syndrome can cause renal injury and hypertension in ALL patients with high WBC count. In this present study, it was found that hypertension was not associated with a higher initial WBC count >50,000 /cumm; OR=0.755 (95% CI 0.25-0.231, p=-0.622), even not associated with hyperleukocytosis OR=0.787 (95% CI 0.22-2.77, p=0.708). A similar finding was reported by Juliansen et al. (2014) indicating, there was no relation between high initial WBC count and hypertension.[17] In this study, renal derangement was found in 17.25% of hypertensive patients, which was not statistically significant. When serum creatinine level was compared among hypertensive patients, at the onset of hypertension with at the onset of induction and at the end of induction, which showed no definite change except for one patient, who had GBS followed by AKI.

The incidence of hypertension in this study was higher among patients who had B cell lineage ALL than T cell lineage ALL interestingly but it was not statistically significant OR=18 (95% CI 0.13-10.61, p=-0.880). In this study, it was found that using treatment regimen B (4 drugs) had no significant allocation for the development of hypertension OR=0.553 (95% CI 0.19-1.64, p=-0.281). Bakk et al (2018) mentioned use of anthracycline has not increased the risk of steroid-induced hypertension during induction.[18] Olger et al (2006) reported that renal leukemic infiltration is a significant risk factor for the development of hypertension, in this study, renal derangement was not found as a risk factor for hypertension.[19] 11 (68.7%) hypertensive patients were found eGFR below normal, which indicates most of the hypertensive patients had reduced initial eGFR. Louis et al (2008) also found low eGFR as a predictor for hypertension in post-chemotherapy increased blood pressure).[7]

A possible explanation may be due to the addition of steroids, various nephrotoxic drugs, hyperhydration, and tumor cell by-products; which act as a compounding factor for the lower renal reserve to the development of hypertension.[7] Incidence of induction toxicities among hypertensive and non-hypertensive patients was comparable in this study except for convulsion, coagulopathy, and febrile neutropenia; indicating patients having convulsion, coagulopathy, and febrile neutropenia developed hypertension more. A possible explanation of hypertension in convulsion is due to subsequent brain oedema and raised intra-cranial pressure following convulsion or alteration of cerebral autoregulation.[20]

TLS, toxicity during induction, associated convulsion, coagulopathy, and febrile neutropenia were statistically significant in univariate analysis. Patients with age <10 years, B cell lineage ALL, and reduced eGFR at diagnosis had a higher percentage of hypertension; which also was identified in various studies. On the contrary, steroids, renal infiltration, obesity, increased glucose, and genetic polymorphisms have been found as risk factors in various studies.

Limitations of the study

The study was limited by a small sample size of the study population. To accurately identify hypertension, additional investigations such as ECG, echocardiography, abdominal ultrasonography, serum cholesterol, and serum triglyceride measurements should have been conducted. Moreover, the study did not detect renal leukemic infiltrations and genetic polymorphisms, which could have provided further insights into the condition.

CONCLUSION

In the current study, the occurrence of hypertension during the induction of remission was observed to be 17.2%. The median age at which hypertension was identified was 4 years. The frequency of hypertension was higher during the second week of induction chemotherapy, gradually declining over the course of the induction therapy period. Notably, hypertension in cases of ALL showed significant associations with other conditions such as tumor lysis syndrome (TLS), febrile neutropenia, convulsion, and coagulopathy during the induction phase.

Recommendations

Regular blood pressure monitoring should be an important part of the induction of remission, especially during the first two weeks of chemotherapy. Further studies will be needed to determine the prognostic significance of hypertension during induction remission period for long term survival and progression to renal parenchymal disease and cardiovascular disease. Wide spectrum studies will be required throughout the whole period of chemotherapy for further identification of risk factors for hypertension in childhood ALL.

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