January 2017

Clinical profile and short-term outcome of pediatric hyperleukocytic acute leukemia from a developing country

Syed Ali Shazif Baqari
Aga Khan University

Anwarul Haque
Aga Khan University

Muhammad Shamvil Ashraf
Aga Khan University

Muhammad Matloob Alam
Aga Khan University

Zehra Fadoo
Aga Khan University

SHORT COMMUNICATION

Clinical Profile and Short-Term Outcome of Pediatric Hyperleukocytic Acute Leukemia from a Developing Country

Syed Ali Shazif Baqari[1], Anwarul Haque[1], Muhammad Shamvil Ashraf[2], Muhammad Matloob Alam[1] and Zehra Fadoo[1]

Abstract

This study was conducted to determine the frequency, clinical profile, and short-term outcome of children with hyperleukocytosis at two pediatric oncology centers in Karachi. Of a total 1,045 patients, 13.97% (n=146) patients had hyperleukocytosis. Majority (61.7%, n=90) were under 10 years of age and 76% (n=146) were male. The symptom duration before diagnosis was more than 30 days in 49.3% (n=72). The median WBC count was 181 x109/L (IQR=130.45-298.3) and extreme hyperleukocytosis (>200 x109/L) was observed in 44.5% (n=65) patients. Majority (94.5%, n=138) of patients were diagnosed with acute lymphoblastic leukemia. One or more complications developed in 78% (n=114) of cases. Clinical and laboratory tumor lysis syndrome (TLS) was observed in 17.1% (n=25) and 39% (n=57) patients, respectively. Pulmonary and neurological complications related to leukostasis were noted in 9.5% (n=14) and 27.3% (n=40) of cases, respectively. Infectious complications occurred in 23.2% (n=34) patients. The case-specific mortality was 20.5% (n=30). No mortality was related to early complications of hyperleukocytosis.

Key Words: *Acute leukemia. Hyperleukocytosis. Mortality. Children. Tumor lysis syndrome.*

Hyperleukocytosis is a medical emergency and is defined as peripheral blood leukocyte count exceeding 100x10^9/L. Acute hyperlukocytic leukemia (AHL) is reported in 5-22% of children at diagnosis with mortality rate 4-24%.[1-4] Ischemic complications of hyperleukocytosis are related to leukostasis in brain and lung with metabolic complications related to tumor lysis syndrome (TLS).[1] There were only a few published reports on hyperleukocytosis in children.[5] The data on hyperleukocytic leukemia in children from Pakistan is scarce. The aim of this study was to report frequency, severity, clinical presentation, treatment and short-term outcome of all children with AHL in two pediatric oncology centers in Karachi.

Medical records of all eligible participants were retrospectively reviewed to collect the pertinent demographic, clinical and outcome data on structured data collection sheet from 2009 to 2015, after approval from ethical review committee (1234-Peds-ERC). The cohort of AHL was divided into two groups, based on the WBC counts: (Group I - 100-199, Group-II - >200 x10^9/L); primary outcome (group 1 - alive, group II - expired).

The secondary outcomes were defined as occurrence of complications that occurred during the first 14 days after presentation as described by Lowe *et al*.[5] Pulmonary leukostasis syndrome was defined as the triad of infiltrate on CXR, tachypnea and hypoxia. Neurological event was defined as any neurological complications that met the National Cancer Institute criteria.[5] Tumor lysis syndrome (TLS) was defined as either laboratory TLS (LTLS) or clinical TLS (CTLS). LTLS was defined as presence of at least two of the features, namely hyperurecemia (serum uric acid >8mg%), hyperphosphotemia (serum phosphorus >6.5mg%), hyperkalemia (serum potassium >6meq/l), and hypocalcaemia (serum calcium <7 mg%). CTLS required the presence of LTLS in addition either one of the three clinical complications, namely renal dysfunction, arrhythmias, features of leukostasis (seizure/intracranial bleed and/or priapism).[2]

After establishing diagnosis of acute hyperleukocytic leukemia, all patients received standard treatment including hyperhydration, allopurinol, cytoreduction and organ-supportive care, as needed. Cytoreduction therapy was performed at the discretion of attending pediatric oncologist. Decision to perform leukapheresis was based on a multidisciplinary team consensus including oncologist, intensivist, and hematologist.

The overall frequency of pediatric oncology patients, who presented with hyperleukocytosis (>100 x109/L) during the study period, was determined by dividing the number of admissions to pediatric oncology patients with hyperleukocytosis with the total number of admissions to the pediatric oncology unit. For analysis, SPSS version 20 (IBM, Chicago, USA) was used. Frequencies with percentages were computed for qualitative variables and mean SD and median (IQR) were computed for

[1] *Department of Peadiatric and Child Health, The Aga Khan University Hospital, Karachi.*
[2] *Department of Peadiatric, Children Cancer Hospital, Karachi.*

Correspondence: Dr. Anwarul Haque, Department of Peadiatric and Child Health, The Aga Khan University Hospital, Stadium Road, Karachi-74800.
E-mail: anwar2haque@gmail.com

Received: February 15, 2016; Accepted: June 20, 2017.

quantitative variables depending whether the data was distributed evenly or skewed, respectively. The risk factors associated with hyperleukocytosis (100-200 x 109/L) and for increased mortality was calculated with Chi-square test for categorical variables and independent t-test used for continuous variables, with p-value ≤ 0.05 was considered significant.

During the study period, 1,045 patients were diagnosed as acute leukemia and 13.97% (146/1045) had hyperleukocytosis at presentation. Majority (94.5%, n=138) of these patients were diagnosed as ALL, of which 44.5% (n=65) had extreme hyperleukocytosis (≤200 x109/L). Patients' demographics, clinical and laboratory characteristics are summarized in Table I. The initial median WBC was 181 x109/L (IQR, 130.45-298.3). The overall incidence was high in age group between 1-10 year (61.7%, 90/146) with male preponderance (76%, 111/146). Duration of illness was >30 days in nearly 50% of patients, indicating late presentation. Majority (74.6%, n=109) patients developed one or more complications in this cohort with infectious complications being the most common (45.2%, n=66). Laboratory TLS developed in 39% (n=57) and clinical TLS was observed in 17.1% (n=25), respectively. The complications related to leukostasis were observed in 2.7% (n=4), 24.6% (n=36) and 22.6% (n=33) as isolated neurological and isolated pulmonary complications and combined neuro-pulmonary complications, respectively. The intensive-care resources were utilized in 26% (n=38), with 20.5% (n=30) and 4.1% (n=6) patients requiring vasoactive-inotropic support for hemodynamics plus mechanical ventilation and mechanical ventilation alone, respectively. Four patients (2.7%) required leukapheresis as a short-term cyoreductive intervention in conjunction with other therapies. Only one patient required intermittent hemodialysis for acute kidney injury due to clinical TLS. The case-specific mortality in this cohort was 20.5% (n=30). Cytogenetic studies were performed on 90 patients and translocations were identified in 18 patients, involving BCR-ABL (9.6%, n=14), MLL gene rearrangement (2.1%, n=3) and Tel AML 1 (2.7%, n=1).

When comparing hyperleukocytosis with extreme hyperleukocytosis, we found significant differences in uric acid, serum potassium and serum creatinine (Table I). When comparing the outcome of patients with hyperleukocytosis in terms of alive or expired, we found need of vasoactive-inotropic support for hemodynamics plus mechanical ventilation, infectious, respiratory and CNS complications significantly associated with increased mortality (Table II).

This is the first comprehensive report on children with hyperleukocytic acute leukemia presenting at two major pediatric cancer centers of Karachi, Pakistan. Few studies have been published on clinical profile and outcomes of children with acute leukemia in children from Pakistan.[6] The frequency of hyperleukocytosis was 14% with two-thirds of children being less than 10 years of age, which is similar to other reports.[2-5] Majority were males (76%, n=111), similar to Lowe *et al* in which 64% were found to be males.[5] Half of the patients in this study had duration of illness of more than 30 days before presentation, which represent late recognition and referrals, resulting in delayed diagnosis. This may lead to progression of disease, development of complications and poor outcome in children with cancer. Most of children 94.5% (n=138) had acute lymphoblastic leukemia in this cohort as compared to 14.5% in the report of Bakhshi *et al*.[2] Hyperleukocytosis was seen more in patients with T-cell ALL (50.9%), which is consistent with other pediatric reports.[3,4]

In this study, the rate of complications of leukostasis (both neurological and pulmonary) were similar to other published reports in literature.[2] Only one patient presented with priapism in this study, which did not require any urological surgical intervention. Both clinical and laboratory TLS were observed in one-quarter of patients as reported by Kulkarni *et al*.[4] Hyperuricemia was the most common metabolic abnormality (32.2%, n=47) observed, which is related to rapid destruction of leukemic blast cell that results in acute renal dysfunction. However, only one patient required intermittent hemodialysis for brief duration. The frequency of pulmonary and neurological insults, secondary to leukostasis in children with acute leukemic hyperleukocytosis, varies from 4% to 20% in different pediatric reports.[2,3] Recently, Kong *et al*. reported 10% and 4% of neurologic and pulmonary complications in their cohort of childhood acute lymphoblastic leukemia with hyperleukocytosis, respectively.[4] Lowe *et al*. reported 6% and 9% of neurologic and pulmonary injuries due to leukostasis in their cohort, respectively. However, there was no difference in the incidence of pulmonary complications between two groups. Most of the presently reported patients required only hyper-hydration, allopurinol and chemotherapy along with intense monitoring. The leukapheresis was done only in 4 cases without any complication. Despite being invasive, this procedure is a safe and effective if performed by experienced staff.

A very high frequency of infection-related complications was observed during the induction-remission phase, consistent with the fact that sepsis has been identified as a major cause of morbidity and mortality in children with cancer. This highlights the importance of education and training in preventing, recognizing and treating infections in such high-risk group.

The mortality rate was 20.5% (n=30) in this cohort. The early mortality in children with hyperleukocytic acute leukemia has been reported to be 4% to 27%.[2-5] There

Table I: Patients' characteristics of acute hyperleukocytic leukemia.

Characteristics	All N=146 (%)	100,000-200,000 N=81 (%)	>200,000 N=65 (%)	p-value	RR (95% CI)
Age					
1-10 years	90 (61.7%)	50 (61.7%)	40 (61.7%)	0.068	-
>10 years	56 (38.4%)	31 (38.3%)	25 (38.5%)		
Gender					
Male	111 (76%)	61 (75.3%)	50 (76.9%)	0.848	0.915
Female	35 (24%)	20 (24.7%)	15 (23.1%)		(0.425-1.970)
Diagnosis					
Pre B cell ALL	61 (41.8%)	40 (49.4%)	21 (32.3%)	0.156	-
T cell ALL	77 (52.7%)	38 (46.9%)	39 (60%)		
AML	5 (3.4%)	2 (2.5%)	3 (4.6%)		
CML	3 (2.1%)	1 (1.2%)	2 (3.1)		
Duration of illness before diagnosis					
1-10 days	26 (17.8%)	13 (16.0%)	13 (20%)	0.858	-
10-30 days	48 (32.9%)	27 (33.3%)	21 (32.3%)		
>30 days	72 (49.3%)	41 (50.6%)	31 (47.7%)		
CNS					
I	127 (87%)	68 (84%)	59 (90.8%)	0.067	-
II	2 (1.4%)	0 (0%)	2 (3.1%)		
III	17 (11.6%)	13 (16%)	4 (6.1%)		
Therapeutic Intervention					
Hydration + Steroids	138 (94.5%)	78 (96.3%)	60 (92.4%)	0.065	-
Hydration + Steroids + Leukapheresis	3 (2.1%)	0 (0%)	3 (4.6%)		
Others	5 (3.4%)	3 (3.7%)	2 (3%)		
ICU Interventions					
Mechanical Ventilation	6 (4.1%)	1 (1.2%)	5 (7.7%)	0.106	-
Mechanical Ventilation + Inotropes	30 (20. 5%)	15 (18.5%)	15 (23.1%)		
Mechanical Ventilation + Inotropes + RRT	1 (0.7%)	0 (0%)	1 (1.5%)		
Inotropes	1 (0.7%)	1 (1.5%)	0 (0%)		
None	108 (74%)	64 (79%)	44 (67.7%)		
Laboratory Data					
Hemoglobin (mg/dl) mean (+/- SD)	7.44 (2.38)	7.1 (+/-2.51)	7.83 (+/-2.16)	0.071	-0.720 (-1.482-0.073)
WBCs (/cmm) median (IQR)	181 (130-298)	132.6 (117.1-163.7)	310.7 (243-404)	<0.001	-
Platelets (/cmm) median (IQR)	30 (18-60)	31 (18-54.5)	29 (19.5-65.5)	0.516	-
LDH (IU/L) median (IQR)	3184 (1681-6347)	2668 (1313-5704)	3517 (2193-7005)	0.289	-
Uric Acid (mg/dl) median (IQR)	5.9 (3.97-9.2)	5.19 (3.47-7.4)	7.31 (4.68-11.57)	0.002	-
Potassium (meq/L) mean (+/- SD)	4.03 (±0.75	3.86 (+/-0.57)	4.23 (+/-0.89)	0.004	-0.371 (-0.623- -0.119)
Phosphorus (mg/dl) mean (+/- SD)	4.3 (±2.02)	4.11 (+/-1.39)	4.51 (+/-2.53)	0.269	0.459 (-1.107-0.310)
Calcium (mg/dl) mean (+/- SD)	8.9 (±0.91)	8.9 (+/-0.89)	9.0 (+/-0.95)	0.822	0.036 (-0.355-0.282)
Creatinine (mg/dl) median (IQR)	0.6 (0.5-0.8)	0.60 (0.47-0.77)	0.63 (0.54-0.98)	0.028	-
Complications					
Respiratory	49 (33.6%)	24 (29.6%)	25 (38.5%)	0.293	0.674 (0.338-1.344)
CNS	14 (9.6%)	3 (3.7%)	11 (16.9%)		0.189 (0.050-0.709)
Infectious	66 (45.2%)	38 (46.9%)	28 (43.1%)		1.168 (0.605-2.252)
Renal	32 (21.9%)	14 (17.3%)	18 (27.7%)		0.546 (0.247-1.204)
Outcome					
Alive	116 (79.5%)	66 (81.5%)	50 (76.9%)	0.541	1.320
Dead	30 (20.5%)	15 (18.5%)	15 (23.1%)		(0.590-2.951)

ALL = Acute lymphoblastic Leukemia; AML = Acute Myeloginous Leukemia; CML = Chronic Myeloginous Leukemia; CNS = Central Nervous System; ICU = Intensive Care Unit; RRT = Renal Replacement Therapy; WBC = White Blood Cells; LDH = Lactate Dehydrogenase.

Table II: Risk factors of mortality among hyper leukocytosis patients.

Characteristics	Alive N=116 (%)	Expired N=30 (%)	P-value	RR (95% CI)
Age				
1-10 years	73 (62.9%)	17 (56.7%)	0.345	-
>10 years	43 (37.1%)	13 (43.3%)		
Gender				
Male	90 (77.6%)	21 (70%)	0.472	1.484
Female	26 (22.4%)	9 (30%)		(0.606-3.629)
Diagnosis				
Pre B cell ALL	49 (42.2%)	12 (40)	0.728	-
T cell ALL	59 (50.9%)	18 (60%)		
AML	5 (4.3%)	0 (0%)		
CML	3 (2.6%)	0 (0%)		
Duration of illness before diagnosis				
1-10 days	21 (18.1%)	5 (16.7%)	0.858	-
10-30 days	37 (31.9%)	11 (36.7%)		
>30 days	58 (50%)	14 (46.7%)		
CNS				
I	104 (89.7%)	23 (76.7%)	0.022	-
II	2 (1.7%)	0 (0%)		
III	10 (8.6%)	7 (23.3%)		
Therapeutic Intervention				
Hydration + Steroids	109 (94%)	29 (96.7%)	0.849	-
Hydration + Steroids + Leukapheresis	2 (1.7%)	1(3.3%)		
Others	5 (4.5%)	0 (0%)		
ICU Interventions				
Mechanical Ventilation	6 (5.2%)	0 (0%)	<0.001	-
Mechanical Ventilation + Inotropes	2 (1.7%)	28 (93.3%)		
Mechanical Ventilation + Inotropes + RRT	1 (0.9%)	0 (0%)		
Inotropes	1 (0.9%)	0 (0%)		
None	106 (91.4%)	2 (6.7%)		
Laboratory Data				
Hemoglobin (mg/dl) mean (+/- SD)	7.49 (+/-2.35)	7.26 (+/-2.51)	0.645	0.225 (-0.741-1.192)
WBCs (/cmm) median (IQR)	180 (130.8-293.7)	218 (123.2-350)	0.418	-
Platelets (/cmm) median (IQR)	31 (19-62)	22.5 (15-42.25)	0.092	-
LDH (IU/L) median (IQR)	3158.5 (1740.5-5115)	4897 (1125-7100)	0.600	-
Uric Acid (mg/dl) median (IQR)	5.7 (3.9-8.36)	7.6 (4.5-15.05)	0.065	-
Potassium (meq/L) mean (+/- SD)	4.08 (+/-0.77)	3.85 (+/-0.68)	0.168	0.229 (-0.077-0.555)
Phosphorus (mg/dl) mean (+/- SD)	4.39 (+/-1.98)	3.9 (+/-2.15)	0.309	0.459 (0.431-1.351)
Calcium (mg/dl) mean (+/- SD)	8.9 (+/-0.89)	9.2 (+/-1.01)	0.176	-0.296 (-0.732-0.139)
Creatinine (mg/dl) median (IQR)	0.61 (0.5-0.8)	0.56 (0.43-0.9)	0.447	-
Complications				
Respiratory	31 (26.7%)	18 (60%)	0.001	0.243 (0.105-0.562)
CNS	8 (6.9%)	6 (20%)	0.041	0.296 (0.094-0.933
Infectious	43 (37.1%)	23 (76.7%)	<0.001	0.179 (0.071-0.453)
Renal	25 (21.6%)	7 (23.3%)	0.833	0.903 (0.347-2.345)
WBCs				
100,000-200,000/cmm	66 (56.9%)	15 (50%)	0.541	1.320
>200,000/cmm	50 (43.1%)	15 (50%)		(0.590-2.951)

ALL = Acute lymphoblastic Leukemia; AML = Acute Myeloginous Leukemia; CML = Chronic Myeloginous Leukemia; CNS = Central Nervous System; ICU = Intensive Care Unit; RRT = Renal Replacement Therapy; WBC = White Blood Cells; LDH = Lactate Dehydrogenase.

was no mortality related to acute metabolic complications or secondary to leukostasis in early phase of cytoreduction. Many deaths in this study could have been prevented by strict implementation of infection control policy in hospital and prompt broad spectrum antibiotics.

Acute hyperleukocytic leukemia in children is not uncommon and can be managed with appropriate supportive care and monitoring. Most of the deaths were related to sepsis during induction-remission phase of chemotherapy instead of early complications of hyper-leukocytosis.

REFERENCES

1. Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: practice management. *Blood Rev* 2012; **26**:117-22.
2. Bakhshi S, Singh RB, Munot K, Pathania S. Complications of "very high" leukocytosis in pediatric acute leukemia patients managed without rasburicase and leukapheresis. *Indian J Pediatr* 2014; **81**:817-20.
3. Kong SG, Seo JH, Jun SE, Lee BK, Lim YT. Childhood acute lymphoblastic leukemia with hyperleukocytosis at presentation. *Blood Res* 2014; **49**:29-35.
4. Kulkarni KP, Marwaha RK. Childhood acute lymphoblastic leukemia with hyperleukocytosis at presentation: perspective and lessons from a tertiary care institution in India. *Asia Pac J Clin Oncol* 2011; **7**:185-7.
5. Lowe EJ, Pui CH, Hancock ML, Geiger TL, Khan RB, Sandlund JT. Early complications in children with acute lymphoblastic leukemia presenting with hyperleukocytosis. *Pediatr Blood Cancer* 2005; **45**:10-5.
6. Mushtaq N, Fadoo Z, Naqvi A. Childhood acute lymphoblastic leukaemia: experience from a single tertiary care facility of Pakistan. *J Pak Med Assoc* 2013; **63**:1399-404.