

Profile and Outcome of Hyperleukocytosis in Childhood Acute Lymphoblastic Leukemia: Experience From a Tertiary Center in India

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ABSTRACT

Hyperleukocytosis is an important cause of morbidity and mortality among acute leukemia patients. The data on hyperleukocytosis from this part of world is scarce. We therefore retrospectively reviewed the clinical and morbidity profile of childhood acute leukemia presenting with total leucocyte count (TLC) >100,000 over a duration of about 2.5 years at our center. Of 140 acute leukemia patients, 24 had hyperleukocytosis at presentation. All 24 patients were of lymphoid lineage. The Mean TLC was 193539(+ 92078)/microlitre, and TLC was >200000/microlitre in 16(66.67%) patients. Tumor lysis was present in 12(50%) patients, while superior mediastinal syndrome was present in 4(16.67%). Features of leukostasis were present in 6(25%) patients (2 had neurological involvement, 3 had pulmonary involvement and 1 had features of both pulmonary & neurological stasis). Renal functions were deranged in 5(20.83%) patients. Further, 11(45.8%) patients had hemorrhagic complications. All 24 patients received hyper hydration, sodium bicarbonate and allopurinol. Chemotherapy was initiated once metabolically stable. One patient died during the first induction and four relapsed during follow-up. Childhood acute leukemia with hyperleukocytosis is associated

with significant morbidity which can be managed with immediate hospitalization, aggressive management with hyper hydration, allopurinol, alkalinization of the urine and intensive monitoring before beginning chemotherapy.

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Key words: Hyperleukocytosis; ALL; Tumor lysis syndrome; Superior mediastinal syndrome

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INTRODUCTION

Hyperleukocytosis, an oncologic emergency is defined as peripheral leukocyte count exceeding 100,000 per microlitre^[1]. It forms a poor prognostic marker for treatment outcome and is an important cause of morbidity and mortality requiring aggressive management. Hyperleukocytosis is seen in 9-13% children with acute lymphoblastic leukemia (ALL); 5-22% children with acute myeloid leukemia (AML) and almost all children with chronic myeloid leukemia (CML) in chronic phase^[2]. Clinically significant hyperleukostasis occurs when the peripheral leukocyte count (WBC) count exceeds 2,00,000/microlitre in AML and greater than 3,00,000/mm³ in ALL & CML^[2,3]. Amongst all hematological malignancies, it is more common in infantile ALL and AML, T-cell ALL with mediastinal mass, hypodiploid ALL and blast phase of CML. These patients are at risk for severe complications from hyperviscosity of blood^[2].

Many children will be asymptomatic. However, children presenting with a WBC count greater than 100,000 per microlitre

should be evaluated for signs and symptoms of leukostasis and the associated complications. The two organs most commonly affected are the lungs and the brain and the symptomatology also reflects this^[1,2]. The children may experience mental status disturbances, headaches, blurred vision, seizures, coma and often resulting in a stroke like presentation, papilledema or retinal artery or retinal vein distension^[1-4]. The pulmonary manifestations of leukostasis and hemorrhage include dyspnea, cyanosis, hypoxia and acidosis^[1,3]. Co-existent superior mediastinal syndrome may mimic these symptoms^[2]. Other symptoms of hyperleukocytosis include gastrointestinal bleeds, priapism/clitoral enlargement, hemopericardium or dactylitis^[1-3]. Cerebral and pulmonary hemorrhages worsen the symptoms of leukostasis. These complications have mortality in the range of 40%, and require emergent treatment before detailed leukemia work-up and referral. Early death in hyperleukostasis is due to CNS hemorrhage or thrombosis, pulmonary leukostasis and metabolic derangements including tumor lysis and renal insufficiency^[2].

There is much debate regarding the appropriate management of this medical emergency, especially about the adequacy of conservative management, and the role of cranial irradiation, exchange transfusion, leukapheresis, hydroxyurea and induction chemotherapy, in isolation or combination. However therapy for hyperleukostasis is tailored towards reduction of blood viscosity (hydration, avoid transfusions & diuretics), alkalisation of urine, allopurinol use and chemotherapy should be started once the patient is metabolically stable^[2]. There is little data, particularly from India, on the incidence, clinical and morbidity profile in childhood ALL and hyperleukocytosis.

Our objective was to study the clinical and morbidity profile of childhood acute leukemia presenting with hyperleukocytosis being treated at the All India Institute of Medical Sciences.

DEFINITIONS

Tumor lysis syndrome (TLS) was diagnosed using Cairo-Bishop criteria for diagnosis of TLS. Cairo-Bishop definition of laboratory tumor lysis syndrome states that 2 or more of the below mentioned criteria should be present, anytime 3 days before to 7 days after starting the induction chemotherapy-

1. Uric acid -4.76 mmol/L (8 mg/dl) or 25% increase from baseline
2. Potassium -6.0 mmol/L (6mEq/L) or 25% increase from baseline
3. Phosphorous -2.1 mmol/L for children, (i.e. 6.5 mg/dl) or 1.45 mmol/L for adults (or 25% increase from baseline)
4. Calcium -1.75 mmol/L (8 mg/dl) or 25% decrease from baseline

Cairo-Bishop definition of clinical tumor lysis syndrome (LTLS) states that the above mentioned criteria plus any of the following criteria should be present-

1. Creatinine: 1.5 ULN (age adjusted)
2. Cardiac arrhythmia/sudden death
3. Seizure

Superior mediastinal syndrome (SMS)/ Superior venecaval syndrome (SVCS) was diagnosed clinically with tachypnea and/or respiratory distress, stridor neck engorgement, facial fullness, snoring, difficulty in deglutition, presence of mediastinal mass with tracheal narrowing confirmed with imaging^[2,3].

Leukostasis in acute leukemia

Pulmonary: Patient may have respiratory distress, hypoxemia, and diffuse interstitial or alveolar infiltrate on chest radiograph. Normal chest radiographs in presence of respiratory distress and/or hypoxia is also well recognized in pulmonary leukostasis.

Neurological: Symptoms include confusion, somnolence, stupor, delirium, coma, headache, dizziness, tinnitus, gait instability, blurred vision, diplopia and visual field defect. On examination—papilledema, retinal vein distension, retinal hemorrhage, occasionally cranial nerve defect and neck stiffness may be found^[2-4].

Renal: Renal failure secondary to tumor lysis, renal vein thrombosis^[2,6].

Coagulation defects: Thrombocytopenia disseminated intravascular coagulation leading to bleeding from various sites e.g. epistaxis, IV catheter, petechial haemorrhage, bleeding per rectum etc.

MATERIALS AND METHODS

Retrospective review of case records of patients of acute leukemia with total leucocyte count (TLC) greater than 100,000/microlitre presenting to the Pediatric Oncology Clinics at the All India Institute of Medical Sciences, from January 2009 to April 2011 were studied. Details of clinical symptoms and physical examination were noted. Details regarding hemogram (total and differential leukocyte count), morphologic characterization of blasts and flow cytometric characterization of lineage were obtained for all patients.

Baseline chest X ray was done to look for mediastinal mass and evidence of pulmonary stasis. Serum biochemistry to monitor for tumor lysis (calcium, phosphate, potassium, uric acid, urine pH), lactate dehydrogenase (LDH) was done in all. Prothrombin time was done for possible coagulopathy and fundus examination was done for papilledema/retinal hemorrhages. Urine output was monitored for all patients.

All children with hyperleukocytosis were admitted into the pediatric wards. All received hyperhydration (3 liters/sq meter intravenous fluids) at admission with allopurinol. Alkalinization of urine was done with sodab carbonate for all patients. All children were monitored according to a hyperleukocytosis monitoring chart. Details regarding respiratory rate, distress, oxygen requirement, pulmonary bleed, tachycardia, change in rhythm. The TLC in all children was monitored twice daily, fluid therapy was modified, blood component therapy given to target a hemoglobin of not greater than 6 g/dl when hemodynamically stable and platelet count of at least 20,000/cubic mm and urine pH monitoring was done for all.

Chemotherapy was started after intravenous hydration was initiated, there were no complications with normal renal parameters and child was metabolically stable with no evidence of septicemia. WBC count, serum electrolytes and renal function were done 12 hourly.

The morbidity profile is described and data analyzed to identify adverse events which include mortality or morbidity in the form of features of leukostasis, coagulopathy, bleeding etc. Data was collected and analyzed using JMP software from SAS. Data was pretreated before analysis. Categorical variables were assigned a numerical value for each category. Continuous variables were examined for any outliers or any other possible mistakes in data gathering. The software is capable of handling missing data. After pretreatment was over, the data was analyzed to correlate the various response variables (hemorrhagic complications, TLS etc) to the various input variables (age, LDH, TLC etc). The regression coefficient (R^2) was used for evaluating the quality of the statistical model. A $R^2 > 0.8$ was considered acceptable for this study. When identifying the parameters that have the significant impact on a given response, those that had p value < 0.05 were considered as relevant.

RESULTS

140 patients were diagnosed with acute leukemia (109 ALL and 31 AML) in the study duration. 24 of these (19 males, 79.2%) had hyperleukocytosis at presentation. Mean (\pm s.d.) age was 7.7 years (\pm 3.3 years). No patient was younger than 1 year, while 8 patients (33.3%) were older than 10 years. B-ALL accounted for 13 cases (54.2%), while T-ALL was found in 9 (37.5%), and 2 patients could not be typed. (Table 1)

Mean TLC (\pm s.d.) was 193539 (\pm 92,078)/microlitre, and TLC was $>200,000$ /microlitre in 16 (66.67%) patients (Table 1). Mean hemoglobin concentration was 6.8 (\pm 2) gm/dL. Mean platelet count was 45,826(\pm 27,925)/microlitre. All patients had thrombocytopenia. 7 (29.17%) patients had platelets 25000 to 50,000, while another 7 (29.17%) patients had platelets $< 25,000$. LDH values were available for 16 patients. Mean LDH was 1,140.6 (\pm 1,014.6) U/dL, and 7 (29.17%) patients had LDH >1000 . Blasts in the CSF were present in one patient. SMS was present in 4 patients (16.7%).

At the time of presentation, renal functions were deranged in 5 patients (20.83%). These 5 patients also had tumor lysis syndrome at presentation. One patient in addition to tumor lysis syndrome also had bilateral renal parenchymal disease with bilateral mild hydronephrosis.

Nine patients had significant respiratory symptoms like dyspnea and/or hypoxia at the time of presentation. Out of these 4 patients (16.7%) had SMS. SMS was significantly more common in T-ALL patients (p value-0.003). All the four patients with SMS also had pericardial effusion and 3 out of these four had concurrent pleural effusion. In addition to these four patients, one other patient also had pericardial effusion. Resultantly, four patients (16.7%) had pulmonary symptoms that could be definitely attributed to leukostasis.

Three patients presented with CNS symptoms (headache, altered sensorium and blurred vision). All three were found to have hemorrhagic stroke on evaluation. All the 3 patients had platelet counts of more than 25,000. One out of these 3 patients also had features of pulmonary leukostasis. Features of leukostasis therefore were present in 6 (25%) patients (2 had neurological involvement, 3 had pulmonary involvement and 1 patient had features of both pulmonary & neurological stasis). These were significantly more common in patients with T-ALL ($p=0.024$).

Eleven patients (45.83%) had hemorrhagic complications, including petechiae, epistaxis, gum bleeds, melena, and stroke. Male patients ($p=0.0048$), those older than 10 years of age ($p=0.0008$), and those with T-ALL ($p=0.0005$) had greater incidence of hemorrhagic complications. It was also seen that higher TLC ($> 2,00,000$ /cumm) and T lineage in combination were associated with higher incidence of hemorrhagic complications ($p=0.0004$).

All 24 patients received hyperhydration (2-3times maintenance) and sodium bicarbonate. Uniform chemotherapy comprising 4 drug induction was started for all. 9 (37.5%) patients required ICU admission and intensive monitoring.

Tumor lysis syndrome was encountered in 12 (50%) patients. Notably, the incidence of tumor lysis syndrome was significantly greater in children with TLC greater than 200,000 per cu mm, as compared to those with TLC $>100,000$ per cu mm.

One patient died during the first induction, due to tumor lysis syndrome and subsequent cardiorespiratory arrest.

On follow up, 7 (29.17%) patients suffered adverse events of relapse or death during follow-up, before completion of chemotherapy course. Of the 3 deaths, two patients died during episode of febrile neutropenia during maintenance, while one

Table 1 Patient characteristics of patients with hyperleukocytosis.

Patient Characteristics	(N= 24)
Mean Age (+SD)	7.7years (+3.3years).
Gender	
Male	19 (79.2%)
Female	05 (20.8%)
ALL subtype	
B-ALL	13 (54.2%)
T-ALL	09(37.5%)
Not typed	02 (08.33%)
Mean TLC (+SD)	193539 (+92,078)/ μ l
Mean hemoglobin (+SD)	6.8(+2) gm/ dL
Mean platelets (+SD)	45826(+27925)/ μ l

died of tubercular meningitis. Four patients relapsed, of whom one is currently in remission, one is scheduled for transplant, and two patients declined further therapy. Leukostatic symptoms at presentation ($p<0.0001$) and hepatomegaly more than 5cm below costal margin ($p=0.0009$) were associated with significantly greater risk of relapse.

DISCUSSION

In our retrospective study, we found around 17% prevalence of hyperleukocytosis in acute leukemia patients. It has been previously reported in 5-30% of the cases of acute leukemia, and in 10-30% of the cases of ALL^[1,7]. Our prevalence of 17.1% is concordant, however all of the patients with hyperleukocytosis in our study had ALL.

Hyperleukocytosis has been reported more commonly in infants, males, and those with T-ALL^[7,8]. We found age greater than 10 years, male sex and T-ALL to be a potential predictor for occurrence of symptoms of hyperleukocytosis i.e. hemorrhage and T-ALL alone for SMS and leukostasis, hence signifying a greater need for aggressive leucoreduction in these subsets.

ALL with hyperleukocytosis commonly presents with metabolic derangements (including tumor lysis syndrome) or disseminated intravascular coagulation, rather than leukostasis symptoms^[7]. These complications have mortality in the range of 40%, and require emergent treatment, before detailed leukemia work-up and referral^[7].

In a study on 178 ALL patients with hyperleukocytosis, Lowe et al (2005) found renal derangements in 5% (9/178) of the patients, with about half of these (4 patients, 2.2%) requiring dialysis^[9]. In a previous study on an Indian pediatric ALL population, Basade et al found deranged kidney function in 44% (5 of 9 patients)^[10]. We encountered a lower percentage of renally impaired patients, and none require dialysis.

Neurological complications were present in 9% (16 of 178) of Lowe et al's study population, which is lower than in our study^[9]. Older age and higher WBC count emerged as significant prognostic indicators of neurological complications, however we did not find any such association.

Lowe *et al* found pulmonary symptoms in only 6% of their patients, with a significantly increased risk in patients with higher WBC count^[9]. Three of these patients required mechanical ventilation^[9]. While we found a comparable occurrence of 8.3% (2/24) of our patients, we did not find any prognostic or predicative factor.

Hemorrhagic phenomena were the most common complication of hyperleukocytosis in our study. Platelet counts were between 10,000 and 20000 in 5 of these patients, while the remaining 3 had platelet counts more than 40,000 per cu mm. Their greater occurrence in male patients, those older than 10 years of age, and those with T-ALL is in concordance with the poorer prognosis associated with these characteristics.

The management of hyperleukostasis hinges on the two critical pegs of leucoreduction and supportive fluid and electrolyte management. In their recent review, Ganzel *et al* (2012) discuss the various strategies to prevent complications in these patients^[1]. Leukopheresis and exchange transfusion are propounded as faster methods to decrease WBC count in hyperleukocytosis^[1,9,11,12]. They are able to reduce WBC counts by 25-50% while also preventing electrolyte imbalances and permitting further blood product support. However, they are encumbered by their invasive nature and risk of complications, more time-consuming, and greater financial and infrastructural cost. Further, there is no unequivocal evidence supporting the efficacy of these aggressive measures, as most of the complications and adverse events occur at presentation, before any therapy can be instituted^[7].

Our patients were all managed with aggressive hydration, alkalisation of urine, and allopurinol administration, along with cytoreduction by induction chemotherapy. There was one mortality during the initial induction phase (4.2%). Previously, many researchers including Lowe *et al*, Castagnetti *et al* (2008), Nelson *et al* (1997) and Basade *et al* (1995), have found conservative cytoreduction to yield effective decline in WBC count and prevention of leukostatic or hemorrhagic complications^[9,10,13,14]. Hyperleukocytosis in leukemia is often complicated by tumor lysis characterized by elevation of serum potassium, phosphorus, and uric acid levels and potentially by decline in calcium levels. Prevention strategies include hydration and prophylactic allopurinol. Prompt measures to reduce serum uric acid to prevent uric acid nephropathy are required. Hyperuricemia can lead to acute renal damage or even failure and should be treated with allopurinol or rasburicase depending on the uric acid levels. Established TLS is managed with the addition of aggressive hydration and diuresis, plus allopurinol or rasburicase for hyperuricemia. Additionally, electrolyte imbalances should be corrected. Whereas allopurinol is the less expensive therapy for hyperuricemia, it only prevents the synthesis of new uric acid. In cases with marked hyperuricemia and TLS, rasburicase (urate oxidase) effectively lowers uric acid levels by enzymatic degradation, even after a single and low-dose application^[15]. The best management of TLS is prevention. Prevention strategies include hydration and prophylactic rasburicase in high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and close monitoring for low-risk patients. Primary management of established TLS involves similar recommendations, with the addition of aggressive hydration and diuresis, plus allopurinol or rasburicase for hyperuricemia^[16]. The use of sodium bicarbonate to alkalinize the urine had historically been recommended as part of TLS prevention and management strategies (eg, when using allopurinol). However, it is not recommended with the use of recombinant urate oxidase (rasburicase). Considering the potential complications associated with alkalinization, such as metabolic alkalosis and calcium phosphate precipitation, and the lack of clear evidence demonstrating benefit, the use of sodium bicarbonate for the prevention and treatment of TLS is currently not recommended^[17,18].

In more recent developments, Ozdemir *et al* (2009) studied the role of continuous low-dose prednisone (6mg/m²/24h) infusion in leukocytoreduction in their randomized control trial on 15 ALL pediatric patients with hyperleukocytosis^[19]. None of the patients developed metabolic or leukostatic complications, suggesting a potential therapy at centers where pheresis and exchange transfusion facilities may not be easily available. Liang *et al* (2011) studied the role of low dose chemotherapy in preventing tumor lysis syndrome in patients with hyperleukocytic acute leukemia^[20]. Patients were treated

with etoposide and cytosine arabinoside at half-doses to reduce WBC count before administering standard induction therapy.

We have found male sex, age >10 years, WBC count >200,000/cu mm and T-ALL as significant factors for prognosis and monitoring in hyperleukocytic acute leukemia patients. In a resource-limited setting, these may allow risk stratification, with more frequent monitoring and prioritizing for more aggressive methods of cytoreduction.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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