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Research Article

Management of Hyperleukocytosis and Results of Leukapheresis in Childhood Acute Leukemia: A Single Center Experience and Review of the Literature

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ABSTRACT

Background: Hyperleukocytosis in pediatric acute leukemia is associated with increased morbidity/mortality and there is no consensus on the use of Leukapheresis (LP) for its management. The aim was to review patients' clinical characteristics and outcomes with newly diagnosed leukemia with Hyperleukocytosis (HL).

Methods: A retrospective case control study reviewed data from a single institution over a 5-year period. Hyperleukocytosis was present in 41 patients with acute leukemia and were included in the study. Treatment strategies included hyperhydration, administration of allopurinol or rasbirucase, early induction of induction Chemotherapy (CT) and LP.

Results: Twenty seven (65.9%) of the 41 patients were male and the median age was 7 (range 1-17) years. LP was used in 9 of 41 (13%) patients with hyperleukocytosis and a total of 25 LP procedures were performed. The mean leukocyte value after apheresis was 65,529/mm^3. In patients with and without LP, tumor lysis syndrome was seen in 2(23%) and 2(6.25%) patients, respectively. Pulmonary leukostasis was seen in 2 patients, one of whom underwent LP. The mean leukocyte count in patients who received LP *vs.* those who did not was 520.000 cells/mm^3 and 158.800 cells/mm^3, respectively (p=0.01). The time from presentation to the initiation of CT was the same between those who received LP and those who did not (mean of 17 h and 18 h) (p>0.05). During the first 30 days after presentation, cerebral leukostasis/coagulopathy or pulmonary leukostasis-related early death did not occur in patients with leukemia.

Conclusions: The use of LP in patients with hyperleukocytosis is safe and effective.

Keywords: Hyperleukocytosis; Leukostasis; Leukapheresis; Acute leukemia; Children

INTRODUCTION

Hyperleukocytosis (HL) is defined as a leukocyte count greater than 100,000 cells/mm^3. Patients who present with HL are at an increased risk of developing symptomatic leukostasis [1]. The organ systems most commonly affected by leukostasis are the lung, central nervous system, gastrointestinal tract and cardiovascular systems. HL is considered an oncologic emergency as it can present as intracerebral hemorrhage or pulmonary stasis and can lead to death.

HL is present at the time of diagnosis in 5% to 20% of patients with acute leukemia. In pediatric acute leukemia, HL is more common in Acute Lymphoblastic Leukemia (ALL) than Acute Myeloid Leukemia (AML). However, children with hyperleukocytic AML are more likely to experience symptomatic leukostasis and metabolic changes related to tumor lysis. Treatment of HL and symptomatic leukostasis involves intravenous hydration, initiation of Chemotherapy (CT) and Leukapheresis (LP). The management of HL-associated tumor lysis also includes hydration, medical management of hyperuricemia with allopurinol or rasburicase, correction of other electrolyte abnormalities and renal replacement therapy [2-6].

LP is a laboratory procedure in which leukocytes are separated from the blood and is a fast and effective method for cytoreduction. Although LP is a very effective method of reducing the number of circulating leukocytes, the association between performing LP and premature death are not clear [7-13]. Although LP is effective in reducing the number of circulating blast cells, its effect is limited as most of the disease occurs in the bone marrow. There are no standard therapy recommendations for LP use. Given the significant resource use, cost and potential complications of LP, randomized studies are needed to evaluate its clinical value.

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In this study, the aim was to describe the characteristics of pediatric patients with acute leukemia presenting with HL, the clinical course of patients who received LP and their outcomes compared to those who did not receive LP.

MATERIALS AND METHODS

Retrospective review was undertaken of all patients with previously untreated acute leukemia who presented to the pediatric hematology and oncology clinic with a White Blood Cell count (WBC) of greater than 100,000 cells/mm^3 between 2017 and 2022. Data collection included diagnostic and laboratory studies and interventions within the first 72 h of diagnosis, results of LP and short-term (30 days) survival outcomes. Demographic and laboratory data were recorded within 72 h of admission to the hospital, at the time of diagnosis.

Consent for publication was obtained from the legal guardians of the patients, including informed written permission for the use of personal or clinical details along with any identifying images to be published in this study. This study was approved by the hospital ethics committee of BaSakSehir Cam and Sakura City Hospital Ethical Committee [14-18].

Articles published between 1983 and 2023, that described diagnosed with acute leukemia with hyperleukocytosis, with a pediatric study population were identified in a systematic review. Using the keywords, “hyperleukocytosis”, “leukostasis”, "leukapheresis”, “acute leukemia”, "chidren" an electronic literature search was performed in Medline and PubMed databases.

Studies were included if they reported hyperleukocytosis in acute leukemia. All studies were checked for references to additional studies and each article identified from the database was compared, to verify matching and exclude duplication. The corresponding author first reviewed the abstracts to confirm eligibility and selected articles were processed for full-text analysis. Any discrepancies identified were discussed with a second author and a consensus decision was reached.

Statistical analysis

Statistical description and comparison were performed using International Business Machine (IBM) Statistical Package for Social Sciences (SPSS), version 22 (IBM Inc., Armonk, NY, USA). Statistical analysis was performed utilizing Fisher’s exact or t-test. Logistic regression was used to generate odds ratios and 95% confidence intervals. P-values<0.05 were considered statistically significant. Significance was evaluated at the p<0.05 level.

RESULTS

Patient characteristics

During the study period, 350 children were diagnosed with acute leukemia, of whom 41 (11.7%) had HL. The mean age among the 41 wit HL was 7.6 (range 1-17) years and 27 (65.9%) were male. The mean age was 7.6 years (range 2-13) in the LP group and 6.7 years (range 1-17) in the non-LP group. Nine (22%) of the patients were diagnosed with AML and 32 (78%) were diagnosed with ALL. T (9, 22) cytogenetic anomaly was detected in only one of the cases diagnosed with ALL (Table 1). The mean time from presentation to starting CT was 17 (6–20) hours in the LP group and 18 (6–21) hours in the non-LP group (p>0.05). The clinical presentation of these patients is shown in (Table 1).

Table 1: Characteristics of patients.

Characteristics	LP group	Non-LP group	Total
Mean age* (years)	7.6 ± 5 (2, 13)	6.7 ± 5 (1, 17)	7.6 ± 4.8 (1.17)
Male	7 (77%)	20 (62.5%)	27 (65.9%)
Female	2 (23%)	12 (37, 5%)	14 (34.1%)
Immunophenotype, n (%)			
ALL	7 (77%)	25 (78, 1%)	32 (78%)
AML	2 (23%)	7 (21, 9%)	9 (22%)
Cytogenetics, n (%)			
Abnormal	0	1 (3.1)	1 (2.4)
Normal	9 (100)	31 (96.9)	40 (97.6)
WBC (cells/mm^3)	520,000	44 (36)	44 (36)
(168.0, 844.0)	158,800	44 (36)	44 (36)
(101.0, 430.0)	238,146	44 (36)	44 (36)
(101.0, 844.0)	44 (36)	44 (36)	44 (36)
Uric acid	8 (2.5, 16)	7 (1.8, 10.7)	7 (1.8, 16)
Potassium	4 (2.5, 5)	6 (7.9, 10.3)	5 (2.5, 10.3)
Phosphorus	3 (1.7, 5.5)	4 (1.1, 6.2)	4 (1.1, 6.2)
Calcium	9 (7.9, 10.5)	8 (3, 10.5)	8 (3, 10.5)
Findings, signs and symptoms, n (%)			
Neurologic leukostasis	0 (0)	0 (0)	0 (0)
Pulmonary leukostasis	1 (11)	1 (3.1)	2 (4.9)
Tumor lysis syndrome	2 (23)	2 (6.25)	4 (9.8)
Treatment,			
Rasburicase, n (%)	3 (33, 3)	3 (9, 3)	6 (14.6)
Mean (range) time to CT (hours)	17 (6, 20)	18 (6, 21)	17.5 (6.21)
Initial stay in PICU, n (%)	9 (100)	4 (12.5)	13 (31.7)
Mean (range) LOS PICU	4, 22 (2, 7)	18 (4, 55)	-
30-day mortality	0	0	0

Note: ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; CT: Chemotherapy; LOS: Length of Stay; PICU: Pediatric Intensive Care Unit; WBC: White Blood Cell Count; LP: Leukapheresis.

Characteristics and laboratory findings during episodes of hyperleukocytosis and leukapheresis results

Nine of these 41 patients (13%) received LP. The mean leukocyte count in the leukapheresis group was 520.000 cells/mm^3 (range 168.000-844.000 cells/mm^3) and 158 cells/mm^3 (range 101.000-430.000 cells/mm^3) in the other group (p=0.01). A total of 25 LP procedures were performed in the nine patients, with a mean of 2.77 procedures per patient. Eight of the patients underwent leukapheresis for prophylactic purposes and the other was therapeutic. In the single patient who underwent therapeutic LP, the indication was dyspnea. There was a mean decrease of 454,629/mm^3 in leukocyte count after LP. The mean leukocyte value before the first apheresis was 520,000/mm^3 and this reduced to a mean of 65,529/mm^3 after the procedures. Neurologic leukostasis, such as vision changes, altered mental status, intracranial hemorrhage was not seen in in the LH group and other group. One of the LH group and 1 of the other group had pulmonary leukostasis, such as dyspnea, hypoxia, respiratory failure (p>0.05). Tumor lysis syndrome was seen 2 patients (23%) in the LP group and 2 patients (6.25%) in the non-LP group (p>0.05). Rasburicase treatment was used in 3 patients in each group. Allopurinol was used in the treatment of all other patients. The mean duration of Intensive Care Unit (ICU) stay was 2 (2-7) days [19-22].

Mortality and complications outcomes

The LP procedure was well tolerated and no life-threatening complications were observed in any patient. During the first 30 days after presentation, early death did not occur in patients with leukemia. (Table 2).

Table 2: The initial presentation and outcomes of patients in the leukapheresis group.

No	Age	Sex	Diagnosis	LSS	TLS	Initial WBC (cells/mm^3) (cells/mm^3) (cells/mm^3)	number of LP	PICU output	Time to CT, first 24 h	LOS PICU (days)	Status
1	5	M	B-ALL	-	-	844	4	346	+	3	Alive
2	13	F	AML-M5	-	-	302	2	84	+	4	Alive
3	11	M	AML-M2	dyspnea	-	168	2	30	+	4	Alive
4	10	M	T-ALL	-	-	503	6	49	+	7	Alive
5	2	M	T-ALL	-	+	560	3	2.5	+	4	Alive
6	7	M	T-ALL	-	-	600	2	3.4	+	4	Alive
7	2	M	T-ALL	-	-	701	3	4.2	+	7	Alive
8	12	F	T-ALL	-	+	693	1	1.5	+	3	Alive
9	12	F	T-ALL	-	+	693	1	1.5	+	3	Alive

Note: ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; CT: Chemotherapy; F: Female; M: Male; LP: Leukapheresis; WBC: White Blood Cell count, TLS: Tumor Lysis Syndrome; LSS: Leukostasis Signs and Symptoms; PICU: Pediatric Intensive Care Unit; CT: Chemotherapy; LOS: Length of Stay.

DISCUSSION

HL is an oncological emergency in pediatric patients with acute leukemia. It has been shown that the risk of mortality increases when neurological/pulmonary leukostasis develops. LP is recommended in leukostasis or when the WBC is elevated, but there is no definite consensus on the management of these patients. It has been suggested that LP should be performed when the WBC exceeds 400,000 cells/mm^3. However, other authors suggested that LP could not be applied to any patient, regardless of the WBC, since it could not be performed in this particular center and no patient loss was experienced, despite the inability to use LP. In the present study, the WBC of patients who underwent LP was >300,000 cells/mm^3 with one exception. In the exception, who had dyspnea, the WBC was 168,000 cells/mm^3 when they underwent LP. When the patients who did not have LP were examined, the WBC was >300,000 cells/mm^3 in only two patients. When both the LP and non-LP groups were examined, no death was observed in the first month of follow-up and there were 32 (78.05%) patients in the non-LP group. In addition, after LP, the WBC decreased from a mean of 510,000 cells/mm^3 to 65,000 cells/mm^3, a decrease in the mean WBC of 87.3%, demonstrating the efficacy of LP. Although LP treatment appears effective and safe, treatment of HL is possible with only hydration support, administration of allopurinol/rasburicase, early initiation of treatment for the disease within the first 24 hours and close clinical follow-up.

There are studies reporting that LP does not delay the duration of CT. This is supported by the results of the present study, as there was no difference in the initiation time of CT, in patients who received LP *versus* those who did not.

Increasing age, male gender and T-cell ALL phenotype are reported to be predictors for LP. In our study, age, male gender and T-cell ALL phenotype were associated with an increased probability of LP, in keeping with the literature.

The clinical symptoms of leukostasis increase the likelihood of requiring LP. In our study, no neurological leukostasis was observed and LP was used in one patient with pulmonary leukostasis, but not to another patient. Both patients survived, but the patient who did not undergo LP required a 55-day stay in the Pediatric Intensive Care Unit (PICU), while the patient who underwent LP only required a seven day stay in PICU. The WBC in these two patients was 202,000 cells/mm^3 and 168,000 cells/mm^3, respectively. It should be noted that the patient who did not undergo LP was an infant and was diagnosed with AML, which may also have had an effect on the prolongation of the length of stay in PICU.

Complications related to LP use have been reported, such as hemodynamic changes, electrolyte irregularities, bleeding due to anticoagulation use and risks associated with central lines. However, no significant complications were reported in the present study, as in similar previous studies.

A summary of the literature regarding LP results in children with HL who are admitted to the hospital with acute leukemia. The common feature of all these studies is that the case group consisted of new diagnosis cancer patients in the pediatric age group. In these reports, LP results were investigated. According to the study results, LP is generally indicated as an effective and safe option.

In the management of patients with HL, prompt and coordinated intervention is required to assess the patient's risk and prevent complications. The effectiveness of LP treatment is usually temporary. The number of blasts in the peripheral circulation may increase rapidly shortly after the procedure. The standard treatment for patients with acute leukemia with HL is supportive therapy and induction CT, in addition to LP. To prevent rebound leukocytes and blasts, cytoreductive therapy, such as the use of hydroxyurea and/or induction CT, should be initiated rapidly.

The limitations of our study are the small cohort size and its retrospective design. Future works should consider looking prospectively at the role of leukapheresis in hyperleukocytic acute leukemia.

CONCLUSION

This study has shown that LP is a procedure that provides an effective reduction in leukocyte count in patients presenting with acute leukemia with HL and has an acceptable side-effect profile. Since LP appears to be an effective method in reducing the number of circulating leukocytes, it may provide an opportunity for the prevention of hyperviscosity and initiation of induction CT. Treatment strategies included hyperhydration, administration of allopurinol or rasbirucase, early induction of induction Chemotherapy (CT) and LP. The amount of time (mean of 17 hours and 18 hours) between presentation and the start of CT was the same ($p>0.05$). Leukemia patients did not experience cerebral leukostasis/coagulopathy or early death owing to pulmonary leukostasis within the first thirty days of presentation.

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