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ORIGINAL ARTICLE

Clinical Outcomes of Childhood Leukemia with Hyperleukocytosis, without Leukopheresis

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ABSTRACT

Introduction: The condition of hyperleukocytosis in acute leukemia is an emergency situation; however, there is still controversy about whether leukopheresis is a superior treatment in preventing early mortality.
Aim: The purpose of this study was to evaluate the early mortality rates in pediatric leukemia patients with hyperleukocytosis who recieved a conventional cytoreduction method in a healthcare center.
Methods: The files of 25 pediatric acute leukemia patients with hyperleukocytosis, diagnosed at Harran University Pediatric Hematology Department between January 2005 and December 2012, were evaluated retrospectively. The clinical and laboratory findings were recorded. Treatments using cytoreduction, with or without methylprednisolone, were evaluated in terms of early mortality rate and duration of treatment for cytoreduction.
Results: The early mortality rate (12.0%) in our center was similar to that of other centers with the ability to treat patients with leukopheresis (3.8-16%). Cytoreduction with methylprednisolone is a faster treatment method than that without methylprednisolone. Also there were no differences between the patients who survived and were lost in terms of duration for cytoreduction.
Conclusion: Hyperleukocytosis in acute leukemia is considered as an emergency situation and should be managed promptly. Conventional methods for cytoreduction can be used with a similar early mortality rate of the centers with the ability to use leukopheresis.

Key words: leukopheresis, hyperleukocytosis, childhood leukemia

INTRODUCTION

Hyperleukocytosis is defined as a leukocyte count ≥100×10^9/L and acute leukemia is considered as a medical emergency especially in childhood. Early mortality and morbidity may occur during the first two weeks of therapy [1,2]. Hyperleukocytosis can cause tumor lysis syndrome (TLS) and leukostasis [3,4]. Slugging within the blood vessels and blast cell interaction with endothelial cells results in leukostasis and occlusion of the vessels [4,5]. Intracranial hemorrhage and respiratory symptoms may also accompany. Metabolic abnormalities due to TLS and leukostasis are among the leading causes of early mortality in acute leukemia's [6,7,8].

Leukopheresis or exchange transfusion, has been recommended for leukocytoreduction in childhood leukemias in various studies [6,9,10]; however, the overall benefits of cytoreduction by leukopheresis and exchange transfusion are unclear. A lack of the possibility for leukopheresis could increase the probability of the patient dying due to complications from hyperleukocytosis. In this study, we aimed to evaluate the outcomes of noninvasive methods (urinary alkalinization and hyperhydration with or without a low dose of methylprednisolone) for leukocytoreduction.

METHODS

Between January 2005, and December 2012, 168 acute leukemia patients [22 with acute myeloid leukemia (AML) and 146 with acute lymphoblastic leukemia (ALL)] diagnosed and followed at Harran University Department of Pediatric Hematology were evaluated. A total of 25 (12 males and 13 females), out of 27 patients with hyperleukocytosis, were enrolled in this study. One patient refused the therapy and another was transferred to another center where leukopheresis was used for cytoreduction therapy.

Approval was obtained by the ethical committee of Harran University for retrospective data collection of these patients. Age, gender, hepatic/splenic enlargement, lymphadenopathy, and the presence of mediastinal enlargement were recorded. During the first two weeks, the following values were recorded daily: complete blood count, including hemoglobin, platelet counts, and white blood cell counts (WBC); and serum biochemistry parameters, including serum potassium (K), calcium (Ca), phosphorus (P), creatinine (Cre), blood urea nitrogen (BUN), uric acid (UA), and lactate dehydrogenase (LDH). Laboratory parameters, which were abnormal during the first two weeks after diagnosis, were evaluated. Early mortality was defined as mortality occurring during the first two weeks of treatment initiation [2,10]. The early mortality rate and overall mortality during the follow up of the patients were calculated.

Hyperkalemia was defined as a serum K concentration >6 mmol/L, hyperphosphatemia was >6,5 mg/dl, hypocalcemia was <8,4 mg/dl, and hyperuricemia was >7,8 mg/dL [11]. If the creatinin level was increased more than twice of the upper limit of normal for the same age and gender, this was defined as renal failure. Leukemia type was defined according to the patient's blastic morphology and flow cytometry.

Treatment

In our center, St. Jude Total XIII and XV protocols for ALL [12,13], and AML BFM 2004 protocol for AML [14], were used in the treatment of children with leukemia.

Before remission induction therapy, 25 of 27 patients with hyperleukocytosis received cytoreductive chemotherapy. The treatment choices were classified as treatment-1 (urinary alkalinization/hydration without methylprednisolone) and treatment-2 (urinary alkalinization/hydration with 2 mg/kg methylprednisolone).

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 version for Windows. Descriptive analyses (median, range, mean, and standard deviation) were presented for age, duration for treatment response, and laboratory findings. The differences between the treatment groups were evaluated with the Mann-Whitney U test for non-normal distributed datas.

RESULTS

The median age at diagnosis was 6.3 years (range 0.2-16.7). The characteristics of the 25 patients included in this study are shown in Table 1. Twenty-two (88.0%) had splenomegaly, 19 (76.0%) had hepatomegaly, six (24.0%) had mediastinal masses**,** four (16.0%) had ocular fundus findings with venous congestion and papillary stasis, one (4.0%) had diffuse

Table 1. Patient characteristics

Age groups at diagnosis (in years)	n (%)
0-1	3 (12.0%)
1-10	18 (72.0%)
>10	4 (16.0%)
Gender (M/F)	12/13
Immunophenotype	**n (%)**
Pre B cell	8 (32.0%)
T cell	10 (40%)
Mature B cell	1 (4.0%)
Biphenotypic	2 (8.0%)
AML	4 (16.0%)
Metabolic complications	**n (%)**
Hyperuricemia	10 (40.0%)
Hypercalcemia	3 (12.0%)
Hypophosphatemia	3 (12.0%)
Hyperkalemia	0
Hypocalcemia	0
Acute renal failure	1 (4.0%)
CBC	**median (range)**
Hgb (g/dL)	8.6 (4.2-15.0)
Thrombocyte (x109/L)	46 (18-257)
WBC (x109/L)	192 (104-842)
CNS status	
ICH	1 (4.0%)
CNS1	24 (92.0%)
CNS2	0
CNS3	2 (8.0%)
Traumatic	1 (4.0%)

AML: Acute Myelogenous Leukemia, CBC: Complete blood count

Hgb: Hemoglobin, WBC: White Blood Cell, ICH: Intracranial Hemorrhage,

CNS1: no involvement, CNS2: blast present with <5 WBC/µl,

CNS3: blast present with >5 WBC/µl

Traumatic: >10 red blood cell/µl

cervical lymphadenopathy. Only 1 had hematuria, and 4 patients had ecchymosis/ petechia at the time of admission**.** One of the patients had intracranial hemorrhage (ICH). One patient (4.0%) having acute renal failure with a serum creatinine level of 2.2 mg/dl and anuria needed hemodialysis.

Cytogenetic and molecular analyses were performed in only 10 patients according to data revealed from patient files. Four of the 10 patients had numerological abnormalities (1 had hyperdiploidy, 2 had hypodiploidy, and 3 had trisomy) and 3 had translocations [t (1:5), t (1:19), and t (11,19)].

All 25 patients with hyperleukocytosis were treated without leukopheresis. Eleven received treatment-1 and 14 received treatment-2. Two of the 25 patients received recombinant with urate oxidase, while the remaining patients received allopurinol. Only one dosage was needed for 2 patients in order to reduce the level of uric acid.

Twelve patients were lost and 13 patients survived during the median follow-up duration of 0.5 (range 0-7.6) years. Only three (11.1%) patients deceased during the first 15 days of remission induction therapy due to intracranial hemorrhage (n=1) and respiratory distress (n=2). Two of these patients received treatment-1 and one received treatment-2 (Table 2). The patients with ICH died on the first day of diagnosis, without reducing the leukocyte count below 100×10^9/L. The initial leukocyte and thrombocyte counts were 275×10^9/L and 74.9×10^9/L, respectively, and the prothrombin time, activated partial thromboplastin time and INR were 20 seconds, 36 seconds and 1.9 respectively. The characteristics of the deceased 12 patients (3 early, 9 after 15 days) have been shown in Table 2.

The median leukocyte count at diagnosis was 297×10^9/L (range 108-842×10^9/L) for the patients who deceased, and 156×10^9/L (range 104-354×10^9/L) for the survivors (p=0.007). Figure 1 shows the median leukocyte count of the patients according to mortality. Ten of the 12 patients who deceased had leukocyte counts higher than 200×10^9/L.

Twenty-four (96.0%) patients' leukocyte counts were reduced below 100×10^9/L within a maximum of 6 days without leukopheresis. In the treatment-2 group, the median duration of reducing leukocyte counts below 100×10^9/L (median 2 days, range 1-5) were significantly lower than those of treatment-1 group (median 5 days, range: 1-6) (p=0.03).

There were no differences between the patients who were lost and survived in terms of median duration of reducing the leukocyte count below 100×10^9/L [median duration of reducing the leukocyte count below 100×10^9/L for patients lost and survivors were 2 (1-5) and 5 (1-6) days respectively, p=0.469]

Table 2. Characteristics of patients who deceased

Patient no	Sex	Age (Year)	Type of leukemia	Treatment	Initial WBC (x109/L)	Achievement of WBC <100x109/L (Day)	Causes of mortality	Day to mortality from admission
1	M	0.2	Pre-B	2	209	1	Pneumonia	20
2	F	0.5	Pre-B	2	533	2	Respiratory distress	2
3	F	8.8	Pre-B	2	842	6	Sepsis	41
4	F	16.8	Pre-B	2	353	1	Sepsis	18
5	F	1.6	T	1	208	4	Sepsis	22
6	F	6.3	T	1	719	1	Sepsis	45
7	M	6.8	T	2	260	5	Sepsis	45
8	F	9.3	T	2	320	2	Sepsis	33
9	M	16.3	T	2	108	1	Sepsis	51
10	M	1.7	AML	1	275	-	ICH	1
11	F	4.3	AML	1	324	1	Respiratory distress	4
12	F	9.8	AML	1	129	2	Sepsis	43

1: Alkalinization + Hydration, 2: Alkalinization + Hydration + Methylprednisolone
Patients 7 and 8 received rasburicase, the others received allopurinol
ICH: Intracranial hemorrhage, DIC: Disseminated intravascular coagulation, WBC: White blood cell

Discussion

Although there is reported literature data on treatment of pediatric hyperleukocytosis in acute leukemia patients the report are not conclusive [2,3,9,10,15-18].

In the literature, 25% of AML patients and 8 to 18% of ALL patients present with hyperleukocytosis [19-21]. In this study, 18.2% of AML patients and 15.7% of ALL patients were admitted with hyperleukocytosis. Approximately 80% of them had hepatosplenomegaly, 22% had mediastinal masses, and T-cell leukemia accounted for the largest part of the group, as previously reported [22,23]. Intracranial hemorrhage is more common in AML than in ALL, and seen in 2-3% of the patients with leukocyte counts higher than 400×10^9/L [2,3]. In this study, we had one AML patient (4.0%) with ICH whose total leukocyte count was 275×10^9/L.

Twenty-four percent of our patients with hyperleukocytosis showed bleeding symptoms (hematuria and petechia). These patients were thrombocytopenic or had a prolonged coagulation parameter. The incidence of coagulopathy was higher than that of the study in which incidence of coagulopathy was reported as 15% [6].

In this study; the life-threatening metabolic complications were lower compared to previous studies [16,17]. Only one patient underwent hemodialysis and that patient recieved a single dose of urate oxidase, which has the potential to decrease the risk for TLS [24].

In the current study the patients who deceased had higher initial leukocyte counts than those of the survivors. Previous studies also found that higher leukocyte counts confers to a poorer prognosis in patients with AML and ALL [3,6,25].

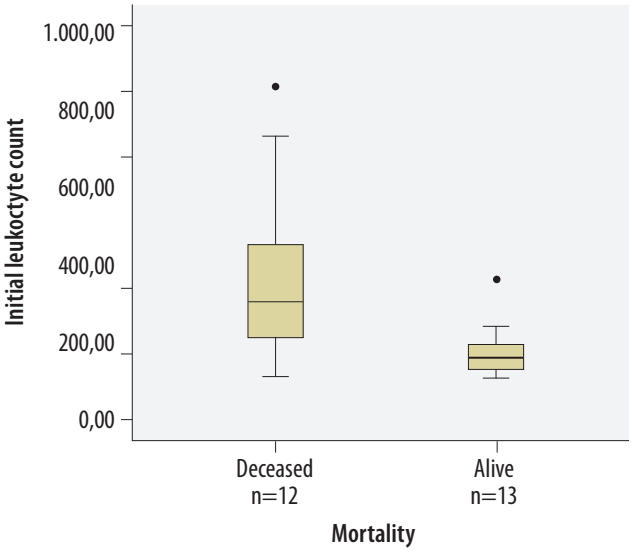

Figure 1. Median initial leukocyte count of patients according to mortality (p=0.007).

In our study, management was sufficient to reduce the leukocyte count below 100×10^9/L, and there were minimal metabolic abnormalities. Maurer et al. showed that the complications of blast cell lysis were managed with acceptable morbidity in a group of patients treated with alkalinization of the urine/hydration [3].

Treatment -2 reduced the blast count more rapidly below 100×10^9/L than treatment 1. However, we found that there were no differences in the duration of leukocyte reduction below 100×10^9/L between the patients who survived and those who deceased. Applying low dose methylprednisolone did not provide an advantage to reducing mortality as in Maurer et al.'s study [3]. However, in one study with continuous intravenous administration of a low dose steroid treatment was recommended to prevent TLS and leukostasis-related complications [17].

In this study, one patient in whom the leukocyte count could not be reduced below 100×10^9/L died with ICH. Chang et al. emphasized that neither leukopheresis nor cranial irradiation were significant in reducing the incidence of ICH in adults [26]. Leukopheresis and exchange transfusion provide rapid reductions in leukocyte counts, and can reduce early mortality, which is defined as the first 15 days of remission induction therapy [2,10,27]. However, there are controversies about the use of leukopheresis. Some studies have shown that it did not have a significant influence on early mortality [27-30]. In a study performed by Porcu et al., it was shown that the degree of cytoreduction with leukopheresis was not correlated with an early mortality rate. Porcu's study also revealed that findings of leukostasis were important for predicting early mortality [29].

On the other hand some other studies showed that leukopheresis could reduce the rate of early mortality to 3.8-16% [2]. In our study, the number of early mortality was 3 (12.0%), which is an average range that could be achieved with leukopheresis.

The independent adverse effects of the T-cell immunophenotype in the mortality of patients with ALL are well-known [6]. As the follow-up duration passes, we may see relapses, especially in patients with T-cell ALL. In this study, only one of the T-cell ALL patients (n=10) was followed up for three years without relapse and the other surviving T-cell ALL patients (n=4) were followed up for less than

one year. We want to emphasize that the long-term follow-up outcomes are not available in the current study, but the early mortality rate was not higher than those of centers, which have the ability to perform leukopheresis.

In conclusion, early mortality rate of the current study was similar (12%) with the early mortality rate of advanced centers with leukapheresis availability (3.8-16%). Low dose methylprednisolone was more effective than urinary alkalinization/hydration alone in reducing the blast count, although there were no differences between the groups who survived and lost in terms of cytoreduction duration. Low dose methylprednisolone plus hydration and urinary alkalinization may be preferred due to the necessity of prompt reduction.

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