

Hyperleukocytosis in childhood acute lymphoblastic leukemia: complications and treatment outcome

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Received: Dec 20, 2005 • Accepted: Jul 25, 2006

ABSTRACT

Hyperleukocytosis, defined as a peripheral leukocyte count $\geq 100 \times 10^9/L$, is seen in 5-20% of newly diagnosed cases of childhood leukemia and is a poor prognostic factor. In this study, we aimed to examine the presenting clinical and laboratory features, complications, and treatment outcome of 47 children with acute lymphoblastic leukemia (ALL) and hyperleukocytosis who were diagnosed and treated in four medical centers of İzmir between January 1990 and January 2001. The median age was 5.0 years (range: 0.1-16.3 years). Median white blood cell count was $495 \times 10^9/L$ (range: $107 \times 10^9/L$ - $794 \times 10^9/L$). Forty-two of 47 patients (90%) had hepatosplenomegaly, 5 (11%) had respiratory distress, 3 (6%) had neurologic symptoms, 3 (6%) had diffuse cervical lymphadenopathy, and 3 (6%) had acute renal failure at admission. Ten of 47 patients (21%) had central nervous system involvement, and 17 (36%) had mediastinal mass. Ten patients (21%) had coagulopathy and 15 patients (32%) had metabolic complications (8 patients had hyperuricemia, 4 had hyperphosphatemia, 2 had hyperuricemia, hyperphosphatemia and hypercalcemia, and 1 had hypocalcemia) before the initiation of therapy. Forty of 47 patients (85%) with hyperleukocytosis were effectively managed with intravenous hydration, alkalization, and allopurinol therapy. Early death during remission induction therapy occurred in 5 patients (11%) with respiratory distress and sepsis. Kaplan-Meier estimates of event free survival and overall survival were 37.0% and 40.5%, respectively.

Key Words: Hyperleukocytosis, lymphoblastic leukemia, survival

Çocukluk çağı akut lenfoblastik lösemisinde hiperlökositoz: komplikasyonlar, tedavi, prognoz

ÖZET

Periferik kanda lökosit sayısının $\geq 100 \times 10^9/L$ olması ile karakterize hiperlökositoz, çocukluk çağı lösemilerinde %5-20 oranında görülebilen ve prognozu kötü olarak etkileyen bir risk faktörüdür. Bu çalışmada, 1 Ocak 1990-1 Ocak 2001 tarihleri arasında İzmir'deki 4 merkezde tanı alıp tedavi edilmiş ve tanı sırasında hiperlökositoz saptanmış 47 akut lenfoblastik lösemili (ALL) çocuğun klinik ve laboratuvar bulguları, gelişen komplikasyonlar ve sağkalımlarının araştırılması amaçlandı. Olguların ortalama yaşı 5.0 yaş (0,1-16,3 yaş) idi. Ortanca beyaz küre sayısı $495 \times 10^9/L$ ($107 \times 10^9/L$ - $794 \times 10^9/L$) bulundu. Tanı anında olguların 42'sinde (%90) hepatosplenomegali, 5'inde (%11) respiratuvar distres, 3'ünde (%6) nörolojik semptomlar, 3'ünde (%6) diffuz servikal lenfadenopati, 3'ünde (%6) akut böbrek yetmezliği bulguları vardı. On olguda (%21) santral sinir sistemi, 17 olguda (%36) mediastinal tutulum mevcuttu. Tedavi başlamadan önce 10 olguda (%21) koagulopati, 15 olguda (%32) metabolik bozukluk (8 olguda hiperürisemi, 4 olguda hiperfosfatemi, 2 olguda hiperürisemi, hiperfosfatemi ve hiperkalsemi, 1 olguda hipokalsemi) saptandı. 40 olguda (%85) intravenöz hidrasyon, alkalinizasyon ve allopurinol tedavisi ile hiperlökositoz kontrol altına alındı. İndüksiyon tedavisinin ilk 15 gününde 5 olgu (%11) respiratuvar distres ve sepsisle kaybedildi. Olguların hastaliksız ve genel sağkalımlarının sırasıyla %37,0 ve %40,5 olduğu saptandı.

Anahtar Sözcükler: Hiperlökositoz, lenfoblastik lösemi, sağkalım

INTRODUCTION

Hyperleukocytosis, defined as a peripheral leukocyte count $\geq 100 \times 10^9/L$, is seen in 5-20% of newly diagnosed cases of childhood leukemia and is a poor prognostic factor since it is usually associated with age less than one year at diagnosis, T-cell immunophenotype, hypodiploidy, and central nervous system involvement^[1-4]. Early metabolic complications such as hyperuricemia, hyperkalemia and hyperphosphatemia secondary to lysis of leukemic blast cells or disseminated intravascular coagulation can seriously complicate the early course of therapy. Early death can be seen in 15-66% of pediatric patients with leukemic hyperleukocytosis^[1,5-7]. Further, among those patients who are in complete remission, relapse rates are higher than observed in those patients with initial leukocyte counts $< 100 \times 10^9/L$ ^[2,3,8]. Recommendations for standard therapy of these patients include adequate hydration, alkalization, control of uric acid production, correction of fluid and electrolyte imbalance, avoidance of excessive transfusions and a careful use of chemotherapeutic agents^[9,10]. Therapeutic leukapheresis, exchange transfusion, or cranial irradiation may be effective in preventing complications of stasis and metabolic disorders in these patients, but their efficacy and utility have not been established^[2,7,11-13].

In this study, we examined the presenting clinical and laboratory features, complications and treatment outcome of children with newly diagnosed acute lymphoblastic leukemia (ALL) and hyperleukocytosis, whose chemotherapy regimens were given at four different pediatric hematology - oncology departments in İzmir, Turkey.

MATERIALS and METHODS

Between January 1990 and January 2001, 522 children up to 18 years of age were newly diagnosed with ALL and treated at four different pediatric hematology - oncology departments (Dokuz Eylül and Ege University Hospitals and Dr. Behçet Uz and Tepecik Teaching Hospitals) in İzmir. The diagnosis of ALL was based on morphologic characteristics of bone marrow leukemic blast cells, classified according to the French - American - British (FAB) criteria, and cytochemical studies^[14]. Immunologic and cytogenetic studies were performed in most of the patients. Children's Cancer Study Group, Pediatric Oncology Group, Dana Farber Cancer Institute

Consortium protocol, or ALL BFM (mostly 90-95) chemotherapy protocols were used^[8,15-18].

Our study sample comprised the 53 (10%) of these 522 patients who had hyperleukocytosis, with leukocyte counts $\geq 100 \times 10^9/L$ at diagnosis. Six of these 53 patients were excluded because of inadequate medical records. Age, gender, clinical and laboratory features, and treatment outcome of those patients were reviewed. Early death was considered if the patient died during the first 15 days of remission induction therapy.

The SPSS program (MS Windows Release 8.0) was used for statistical analysis. The Kaplan - Meier method was used to estimate survival rates. The event free survival (EFS) was calculated from the time of starting chemotherapy to the end of the first remission (relapse or death in first remission) or to the time of analysis. The overall survival (OS) was calculated from the beginning of chemotherapy to death or to the time of analysis. Differences between groups were evaluated by using log-rank tests. A p value of < 0.05 was accepted as statistically significant.

RESULTS

The median age of the 47 patients was 5.0 years (range: 0.1-16.3 years). Fourteen (30%) of them were younger than 2 years old, 16 (34%) were 2-10 years old, and 17 (36%) were older than 10 years. There were no statistically significant differences between the age groups ($p > 0.05$) or between sexes (23 female, 48%; 24 males, 52%) ($p > 0.05$). Forty-two of 47 patients (90%) had hepatosplenomegaly, 5 (11%) had respiratory distress, 3 (6%) had neurologic symptoms (cerebrovascular accidents and frontal headache), 3 (6%) had diffuse cervical lymphadenopathy, and 3 (6%) had acute renal failure. Ten of 47 patients (21%) had central nervous system involvement and 17 (36%) had mediastinal mass. Median hemoglobin level was 8.3 g/dl (range: 3.8-15.4 g/dl) and median white blood cell count was $495 \times 10^9/L$ (range: $107 \times 10^9/L$ - $794 \times 10^9/L$). Ten patients (21%) had disseminated intravascular coagulation consisting of a prolonged prothrombin and partial thromboplastin time, increased fibrin degradation products, and/or low fibrinogen level. Fifteen patients (32%) had metabolic complications before the initiation of therapy as follows: 8 patients (17%) had hyperuricemia, 4 (8%) had hyperphosphatemia, 2 (4%) had hyperuricemia, hyperphosphatemia and hypercalcemia, and 1 (2%) had hypocalcemia.

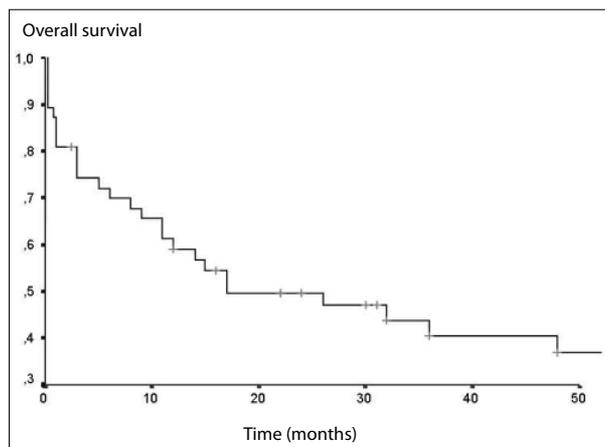


Figure 1. Kaplan-Meier analysis of overall survival of patients with acute lymphoblastic leukemia and hyperleukocytosis

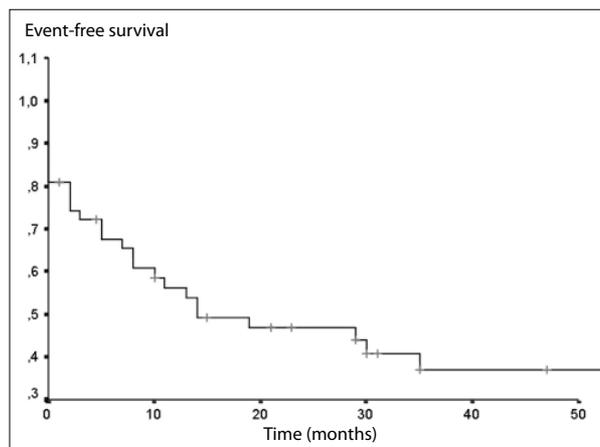


Figure 2. Kaplan-Meier analysis of event-free survival of patients with acute lymphoblastic leukemia and hyperleukocytosis

According to FAB classification, 39 patients (83%) had L1, 7 (15%) had L2, and 1 (2%) had L3 blast morphology. Immunophenotyping could be performed in 30 patients: 15 (50%) were T-cell, 14 (47%) precursor B-cell, and 1 (3%) mature B-cell ALL. Cytogenetic and molecular analysis could be performed in 8 (16%) and 3 (6%) patients, respectively. In three patients, cytogenetic and molecular abnormalities of t(4;11), t(1;19), and t(8;22) were detected; other patients' results were unremarkable.

Forty of 47 patients (85%) with hyperleukocytosis were effectively managed with intravenous hydration, alkalization, and allopurinol therapy. Additionally, 6 patients (13%) needed cyto-reduction via leukapheresis and 1 patient (2%) received cranial irradiation. The leukocyte count decreased to $<100 \times 10^9/L$ in all patients in a mean time of 5.7 ± 2.8 days.

Early death during remission induction therapy occurred in 5 patients (11%) with respiratory distress and sepsis.

Thirty-four of 47 patients (82%) attained complete remission at the 33rd day of induction chemotherapy.

Kaplan-Meier estimates of EFS and OS as given in Figure 1 and Figure 2 were found as 37.0% and 40.5%, respectively.

DISCUSSION

Eight to 18% of pediatric patients with ALL present with hyperleukocytosis^[2,11]. In our study, 10% of pediatric ALL patients had presented with

hyperleukocytosis and those patients had high frequency of organomegaly, central nervous system and mediastinal involvement, and T-cell immunophenotype, as reported in the literature^[1-4]. Coagulopathy (21%), neurologic features (6%), pulmonary leukostasis (11%) and metabolic complications (32%) had been observed before the initiation of chemotherapy. In previous studies, the frequencies of coagulopathy, cerebrovascular accidents, and pulmonary leukostasis in those patients have been reported as 15%, 5%, and 3%, respectively^[2,3,11].

In pediatric ALL patients with hyperleukocytosis, the complications of blast cell lysis and leukostasis were manageable with acceptable morbidity and minimal mortality in a group of patients treated with effective hydration, allopurinol, and alkalization of the urine before initiation of chemotherapy^[11]. This management was also efficient in 40 (85%) of our patients; in 6 (13%) patients in whom symptoms of leukostasis were evident, leukapheresis was also used. The use of leukapheresis to reduce leukemic blast cell burden in children with ALL and hyperleukocytosis is controversial^[2,7,9-13]. Maurer *et al.*^[11] noted a significantly lower incidence of electrolyte imbalances in patients who underwent leukapheresis than in those who did not. Also, leukapheresis had been used mostly in patients with higher leukocyte counts and these patients could have experienced more complications if they were not treated with leukapheresis^[2]. Prospective randomized trials are necessary to evaluate the efficacy and safety of leukapheresis in children with hyperleukocytosis.

Table 1. Event-free survival of children with acute lymphoblastic leukemia and hyperleukocytosis according to different chemotherapy protocols.

| | Age | No. of patients | Event-free survival (5-years) % | Reference no. |
|-------------------|-----|-----------------|---------------------------------|---------------|
| AIEOP-ALL 82-95 | ≤17 | 145 | 37.7 | [20] |
| ALL-BFM 81-95 | ≤18 | 270 | 53.1 | [8] |
| CCG 83-95 | ≤21 | 599 | 60 | [15] |
| Dana Farber 81-95 | ≤18 | 41 | 78.6 | [18] |
| POG ALL 86-94 | ≤21 | 119 | 38.4 | [16] |
| UKALL 80-97 | ≤14 | 252 | 44 | [21] |

In our study, immunophenotyping could be performed in 30 of 47 patients and 50% of them had T-cell ALL. Similarly, half of the patients with hyperleukocytosis had T-cell ALL in a study of Eguiguren *et al.* [2] The independent adverse effect of T-cell immunophenotype is well known, and patients with T-cell ALL had significantly worse outcome than did those with precursor B-cell ALL [19].

Our patients had a remission induction rate of only 82%. Early death occurred in 11% of our patients. EFS and OS were 37% and 40.5%, respectively. Because the experience was drawn from a time period of 10 years and the data was received from four different pediatric hematology-oncology centers, the patient groups were not comparable either in their supportive care

management or in their chemotherapy protocols. Intensive remission induction therapy coupled with an effective and well-tolerated continuation treatment is necessary to improve the outcome of these patients. The results of some trials, which were given to ALL patients with hyperleukocytosis, are given in Table 1 [8,15-16,18,20-21].

Although intensive chemotherapy and supportive care can favorably influence prognosis, pediatric patients with ALL and leukocyte counts of $\geq 100 \times 10^9/L$ have poor outcome. Early deaths due to complications, predominance of T-cell immunophenotype, central nervous system involvement and mediastinal mass at diagnosis are some of the features associated with poor outcome in these patients.

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