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Origial Article

Evaluation of leukapheresis and leukapheresis with additional cytoreduction in acute leukemia with hyperleukocytosis

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A B S T R A C T

Background Hyperleukocytosis is a high-mortality emergency that must be diagnosed and treated promptly. The treatment options are low-dose cytosine arabinoside, hydroxyurea, steroids and leukapheresis. The risks and benefits of leukapheresis and leukapheresis with cytoreductive drugs in hyperleukocytosis are unclear. Therefore, we aimed to evaluate the efficacy of leukapheresis and the effect of adding cytoreductive drugs to leukapheresis in reducing leukocyte count and mortality in our patients.

Material and Methods Thirty-four adult patients with acute leukaemia who underwent leukapheresis were included in this retrospective study.

Results The median age was 66.5 years old, and 88.2% of the patients were acute myeloid leukaemia. The total number of leukapheresis was 69 cycles, and the median number of the procedure was 2. The most common symptoms were associated with the pulmonary system (67.6%). The median follow-up was 17.5 days. The mean reduction of leukocyte count was 69,112/mm3, and the efficacy of leukapheresis was 40.9%. The decrease in leukocyte and platelet counts was statistically significant when compared before and after leukapheresis. The mortality rate was 76.5% during hospitalization. While 24 patients received concomitant cytoreductive drugs with leukapheresis, ten did not. There was no statistically significant difference between these groups regarding reducing leukocyte count, efficiency of leukapheresis and mortality (p values 0.857, 0.562 and 0.553).

Conclusions In our study, we showed the efficacy of leukapheresis in hyperleukocytosis but failed to show any difference in leukocyte reduction or mortality with additional cytoreductive drugs. Leukapheresis with concomitant cytoreduction does not abolish or increase mortality.

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INTRODUCTION

Leukaemias are hematopoietic stem cell-derived clonal malignant diseases that usually manifest with an increased leukocyte count due to the uncontrolled proliferation of malignant cells. Hyperleukocytosis is a severe clinical condition in which the leukocyte count in the peripheral blood reaches > 100,000/mm^3. While 5-13% of patients with acute myeloid leukaemia (AML) have hyperleukocytosis, this rate is 10-30% in patients with acute lymphoid leukaemia (ALL). Hyperleukocytosis, which causes leukostasis, bleeding, respiratory failure, and neurological deficits, has a poor prognosis. Clinical findings related to vascular occlusion, especially in the central nervous and pulmonary systems, are the most common symptoms and are associated with mortality.[1] However, symptoms and complications related to hyperleukocytosis may be encountered below 100,000/mm^3 in some acute leukaemias. Hyperleukocytosis is a poor prognostic factor. Early mortality rates can reach 8% in the 24th hour and 29% in the 1st week, respectively, due to tumour lysis syndrome and disseminated intravascular coagulopathy with leukocytosis and induction treatments.[2-5]

Hyperleukocytosis is a haematological emergency that must be managed carefully and rapidly, from diagnosis to treatment, due to the high mortality rate and associated complications. The decline of leukocyte count is provided as soon as possible to decrease disease burden and hyperleukocytosis complications. Low-dose cytosine arabinoside, hydroxyurea, steroids and leukapheresis application are frequently used for achieving cytoreduction.[6,7]

Leukapheresis is a process in which an apheresis device can quickly achieve leukocyte decrease. In this procedure, blood with a high leukocyte count is taken from the patient and given back by filtration with a decreased leukocyte count. Some studies have shown the benefits of leukapheresis in reducing mortality, tumour lysis syndrome and the risk of bleeding complications in patients with hyperleukocytosis and leukostasis symptoms. In addition, some studies mention the benefits of leukapheresis by stopping blasts in S or G2/M phases, increasing sensitivity to chemotherapy, and increasing the mobilization of these more sensitive blasts from the bone marrow to the peripheral blood.[8-13] However, there are controversial opinions that leukapheresis does not affect or reduce mortality.[14-17] In addition, there are some concerns in using leukapheresises, such as critical thrombocytopenia and anaemia before the procedure, high leukocyte counts that may be encountered after the procedure, and difficulties and complications in establishing vascular access.[17-19]

Leukapheresis application is recommended as a grade 2B and category III recommendation, meaning "weak recommendation" in the 2023 American Society for Apheresis (ASFA) guideline. Also, the guideline offers a personalized treatment decision for hyperleukocytosis, unlike the previous one.[20] The leukapheresis procedure's benefits and risks and cytoreductive treatment addition to leukapheresis are still controversial in acute leukaemias with hyperleukocytosis. Hence we aimed to analyze the efficacy and mortality rates of leukapheresis and the addition of cytoreductive therapy to patients with acute leukaemia who underwent leukapheresis in our centre.

MATERIAL AND METHODS

This retrospective study included 34 consecutive adult patients with AML and ALL who underwent leukapheresis for hyperleukocytosis between July 2015 and December 2022. The ethical approval was obtained from the Institutional Ethical Committee of Trakya University (TUTF-GOBAEK 2023/38). All data were collected from medical records and electronic files.

The leukapheresis process was applied to patients with a leukocyte count above > 100,000/mm3 or hyperleukocytosis-associated symptoms independent from leukocyte count, according to the clinician's decision. Hyperleukocytosis-associated symptoms were confusion, somnolence, focal neurologic symptoms, dyspnea, hypoxia, respiratory distress, visual defects, retinal haemorrhage, tinnitus, acute renal failure and hemorrhagic conditions. The decision of initiation and discontinuation of leukapheresis was determined according to hemodynamic status, cardiovascular comorbidities, coagulation abnormalities, proper vascular access, haemoglobin and platelet count. Patient's gender, age, diagnosis, Charlson comorbidity index21, clinical findings and symptoms, the number of leukapheresis process, haemoglobin, platelet and leukocyte count before and after leukapheresis, complications during the procedure and outcomes were recorded. The decline of leukocyte count and the efficacy of leukapheresis (%) were calculated. The approach's effectiveness was calculated with the formula; the drop of leukocyte count/the leukocyte count before

the procedure x100. The leukapheresis process was applied via the Haemonetics © MCS (USA&Canada) device with centrifugation. The application was made via peripheral or central vascular access, which is appropriate. Concomitant cytoreductive treatment was given, such as cytosine arabinoside, hydroxyurea, 7 + 3 protocol (cytosine arabinoside+idarubicin) in AML patients while vincristin+methylprednisolone in ALL patients. The initiation of cytoreduction medication before or during leukapheresis was admitted as a concomitant cytoreduction treatment. Supportive treatment with hydration, blood transfusion, and allopurinol was also provided, which was appropriate. Calcium supplementation was made for patients who were not contraindicated. Patients followed up during the hospitalization.

Statistical analysis

We used IBM SPSS v21 program for statistical analyses. Continuous variables were shown as the mean ± standard deviation (SD) and categorical variables as percentages. Paired t-test or Wilcoxon test was utilized for comparing groups with continuous variables due to appropriate distribution. Kaplan-Meier analysis (log-rank) was used for mortality. P values less than 0.05 were regarded as significant.

RESULTS

Thirty-four consecutive adult patients with AML and ALL who underwent leukapheresis for hyperleukocytosis were analyzed. The leukapheresis process was applied according to leukocyte count or existing symptoms associated with leukocytosis independent from the leukocyte count unless there was a contraindication. The decision of discontinuation of leukapheresis was given by the clinician according to the patient's clinical and laboratory findings, such as providing adequate decline of leukocyte count, improving symptoms, occurring contraindicated conditions or vascular access problems. 58.8% of the patients were male, and 88.2% were AML. The distribution of the AML patients whose records could be evaluated according to French-American-British (FAB) classification was as follows; 3 patients M0, five patients M1, four patients M2, one patient M3, ten patients M4, two patients M5. Of the subtypes of the remaining patients, one patient was mixed-phenotype acute leukaemia, one was pro-B ALL, and three were T-ALL. According to available genetic data, two patients had nucleophosmin (NPM-1) mutation, one patient had JAK 2 V617F mutation due to the underlying disease of myelofibrosis, and one patient had t (9;22) major p 210 due to chronic myeloid leukaemia history. The mean and median ages were 64.6 years and 66.5 years, respectively. The total number of leukapheresis performed was 69 cycles, and the mean number of leukapheresis was 2.03.

Table 1. Characteristics of patients who underwent leukapheresis with acute leukaemia.

Variables	Values
Age (years)	64.62 ± 13.89
Gender (Male/Female) (%)	58.8/41.2
Diagnosis (AML/ALL) n (%)	30 (88.2)/4 (11.8)
FAB classification (n: 25) n (%)	
M0	3 (12)
M1	5 (20)
M2	4 (16)
M3	1 (4)
M4	10 (40)
M5	2 (8)
Charlson comorbidity index (median)	5
The mean number of leukapheresis	2.03 ± 1.26 (1-7)
The mean leukocyte count before leukapheresis (/mm^3)	153,112 ± 78,825
The mean haemoglobin count before leukapheresis (g/dL)	8.0 ± 1.53
The mean platelet count before leukapheresis (/mm^3)	77,882 ± 93,029
The mean leukocyte count after leukapheresis (/mm^3)	100,161 ± 67,727
The mean haemoglobin count after leukapheresis (g/dL)	7.9 ± 1.35
The mean platelet count after leukapheresis (/mm^3)	54,515 ± 51,776
The mean leukocyte count decrease (/mm^3)	69,112 ± 51,517
The mean efficiency of leukapheresis (%)	40.90 ± 26.19
The mean follow-up time (days)	21.82 ± 16.56 (2-57)
Concomitant cytoreduction (AML/ALL) n (%)	21 (61.7)/3 (8.8)
Outcomes (Exitus/Alive) (%)	76.5/23.5

FAB: French-American-British.

The most common symptoms were associated with pulmonary symptoms such as dyspnea, dry cough, alveolar haemorrhage in 23 patients, impaired vision in 3 patients, headache, and dysarthria in 2 patients. The mean and median follow-up time was 21.82 days and 17.50 days, respectively. The mean reduction of leukocyte count was 69,112/mm^3, and leukapheresis efficiency was 40.9%. The features of the patient group was summarized in Table 1.

In comparing the leukocyte, haemoglobin and platelet count before and after leukapheresis, the decrease in leukocyte count and platelet count were statistically significant ($p < 0.001$ and 0.010, respectively).

Twenty-four patients received concomitant cytoreduction therapy, while ten patients could not receive it due to death or received it after leukapheresis procedures were completed. When we compared the patient groups as received concomitant cytoreduction or did not receive it, the mean leukocyte count decrease was 71,360/mm^3 in the concomitant cytoreduction group while it was 64,286/mm^3 in the other group, and this difference was not statistically significant with a p-value 0.857. The efficiency of leukapheresis was 42.75% in the concomitant cytoreduction group, while it was 36.8% in the other group. This difference was also insignificant, with a p - value of 0.562.

During the follow-up period, the mortality rate was 76.5%. The mean and median survival was 24.9 days (± 3.40, 95% confidence interval-CI) and 18 days, respectively (Figure 1). In comparing the patients who received concomitant cytoreduction and did not receive it, the mean survival was 26.2 days (± 4.22, 95% CI) in the concomitant cytoreduction group. In comparison, it was 20.7 days (± 4.49, 95% CI) in the other group. This difference was insignificant (p = 0.553) (Figure 2).

A catheter occlusion occurred in a patient during the procedure and was terminated. Apart from this, there were no complications related to the leukapheresis procedure.

DISCUSSION

In this study, we showed that the leukapheresis efficiency was 40.9% in patients with acute leukaemia with hyperleukocytosis, and there was no statistical difference between the groups that received and did not receive concomitant cytoreduction in terms of reduction in leukocyte count, leukapheresis efficiency and survival.

Hyperleukocytosis is a haematological emergency encountered in 20% of acute leukaemia, which can progress with leukostasis, tumour lysis syndrome and diffuse intravascular coagulation. The standard treatment approach includes leukapheresis, chemotherapy, supportive treatment and tumour lysis prophylaxis.[7,19] While Zhang *et al.*19 reported the median age as 42 years old in the AML patient group (n: 229) and 27 years old in the ALL patient group (n: 125), Lee *et al.*22 reported that 52 years old and 42 years old in AML patients (n: 212) and ALL patients (n: 97), respectively. Besides that, in these studies, leukapheresis was observed to be mostly applied to AML patients with a rate of over 65%. In a meta-analysis which was included 13 studies and 1,743 patients with AML (486 patients performed leukapheresis and 1,257 patients did not perform leukapheresis), the median age of the patients who underwent leukapheresis was 56.6 years, and they were younger than the group that did not. And in the

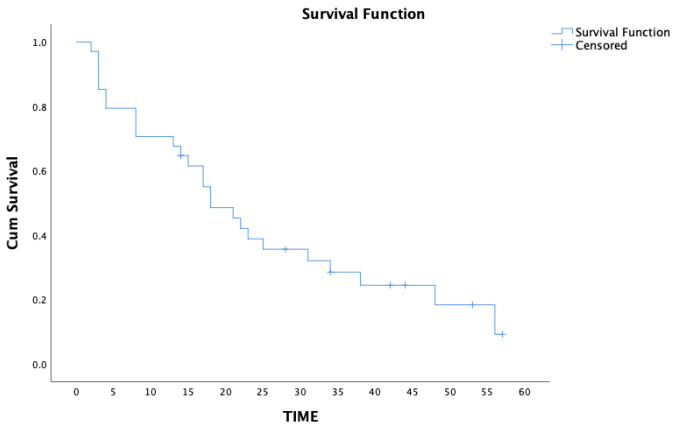

Figure 1. Kaplan-Meier analysis in patient group.

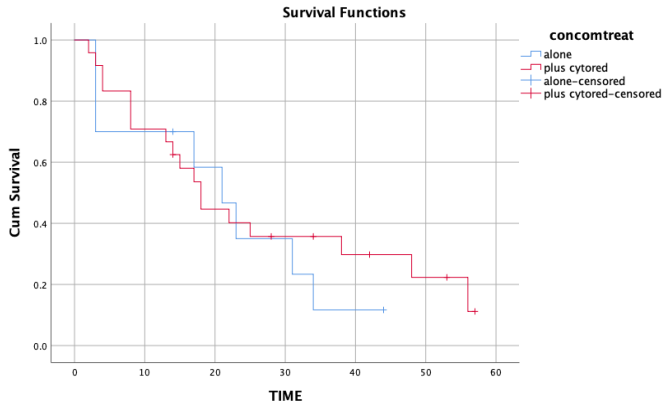

Figure 2. Kaplan-Meier analysis according to receiving of concomitant cytoreductive treatment.

same meta-analysis, the median leukocyte count was 180,900/mm^3 in the performed leukapheresis group, while it was 137,100/mm^3 in the other group.[23] In the study of Zhang *et al*.[19], the median leukocyte count was 103,700/mm^3 in AML patients and 129,800/mm^3 in ALL patients who underwent leukapheresis. In our study, 88.2% of the patients were diagnosed with AML; the median age was 66.5 years old. These results probably differed markedly from the literature due to the clinician's decision of leukapheresis independent from the leukocyte count.

The decrease in leukocytes varies between 20% and 60% with the single application of leukapheresis.[3,24] In some studies, the range of reduction in leukocyte count was between 66% and 20% in AML patients, while it was 71% in ALL patients.10,18,25,26 In another study of 31 patients aged 2 to 77 years with AML, ALL, and chronic myeloid leukaemia, a 39.1% reduction in leukocyte count was achieved in approximately 50% of the patients. At the same time, the remainder did not.[27] Lee *et al*.[22] also reported that the leukocyte reduction count with leukapheresis was significant in both AML and ALL patients. The median leukocyte count was 164,000/mm^3 and 79,100/mm^3 before and after leukapheresis in AML patients, respectively ($p < 0.001$). Pre-leukapheresis leukocyte count was 204,800/mm^3, and post-leukapheresis leukocyte count was 92,100/mm^3 in ALL patients ($p < 0.001$).[22] In the study of Zhang *et al*.[19], which included 229 patients with AML and 125 patients with ALL, and in the study of Jin *et al*.[26] in 67 patients with AML, the decrease in leukocyte count was also significant. In our study, leukapheresis efficiency was 40.9%, and the difference in leukocyte count before and after leukapheresis was statistically significant ($p < 0.001$), similar to the literature. Although leukapheresis is a viable option in the treatment of hyperleukocytosis, auxiliary cytoreductive drugs are needed in the management of hyperleukocytosis due to the transient decrease in leukocyte count and the occurrence of rebound leukocytosis in leukocytosis. Although cytoreductive agents such as hydroxyurea and steroids are less effective in decreasing leukocyte count than leukapheresis, administering these agents is recommended in AML and ALL patients with hyperleukocytosis, respectively.[17,28] Besides contributing to reducing leukocyte count, steroids are thought to inhibit adhesion molecules on blastic and endothelial cells, and hydroxyurea may reduce blood viscosity.[29-31] Zhang *et al*.[19] showed that the combination of hydroxyurea and leukapheresis improved the reduction in leukocyte count, but the efficacy of leukapheresis was not improved in AML patients. In this study, 172 patients were in the leukapheresis with cytoreduction group, while 57 were in the leukapheresis group. The reduction of leukocyte count was 56,890/mm^3 in the combination group and 45,680/mm3 in the leukapheresis group ($p = 0.021$). The efficiency of leukapheresis was 53.48% and 53.74% in leukapheresis and the combination group, respectively ($p = 0.397$). In ALL patients, the administration of dexamethasone did not show any benefits regarding the reduction of leukocyte count and the efficiency of leukapheresis.[19] In our study, we could not show any significant difference between the groups that received and did not receive concomitant cytoreduction therapy regarding leukocyte count reduction or leukapheresis efficiency.

Regarding leukapheresis-related adverse events, haematological toxicities resulting from the collection of contaminated red blood cells and platelets of a similar density of blasts and immature myeloid cells are serious adverse events that are difficult to manage and cause severe complications in acute leukaemias.[9,10,19,26,27] Zhang *et al*.[19] reported that the decrease of haemoglobin and platelet count is the most common in AML patients. Jin *et al*.[26] said a significant decline in platelet, red blood cell, haemoglobin, hematocrit, mononuclear cell and neutrophil levels in the blood tests after leukapheresis. The median blood cell reduction was 28,000/mm^3 in platelet count while 7 g/dL in haemoglobin count.[26] In our study, the decrease in platelet count was significant ($p = 0.010$) at 23,367/mm^3, but the decrease in haemoglobin count was not significant.

The benefits of leukapheresis in terms of early mortality are controversial. Some studies support the idea that leukapheresis reduces early mortality, while others do not.[15-18,32,33] One of two matched-control studies comparing 26 patients with AML with and without leukapheresis showed that leukapheresis reduced early mortality (30.8% vs 57.7%, $p = 0.022$) but did not affect long-term mortality. The other matched-control study could not demonstrate any favourable impact on early mortality in 998 patients with AML.[16,33] Lee *et al*.[22] reported the 30-day survival rates as 86.3% and 94.8% in AML and ALL patients who underwent leukapheresis, respectively. In Choi *et al*.'s study14, a propensity-score-matched analysis (22 matched pairs of patients with AML and 16 matched

pairs of patients with ALL), no statistically significant difference in ≤ 2-week mortality was reported in both AML and ALL with leukapheresis (18% vs 23%, $p = 0.999$). The meta-analysis study of Oberoi *et al.*29, including 20 studies and 1,354 patients with AML, reported the rate of early death (deaths during first induction) as 20.1%, and they failed to show any favourable influence of leukapheresis or hydroxyurea/ low dose chemotherapy on early mortality. Zhang *et al.*19 showed a greater reduction in leukocyte count in AML patients receiving leukapheresis and hydroxyurea simultaneously. However, they could not show any significance regarding leukapheresis efficiency among these patient groups.[19]

Recently, a previously mentioned meta-analysis study reported no evidence of an early mortality benefit of leukapheresis in AML patients. The authors do not recommend the routine use of leukapheresis for hyperleukocytosis in AML patients, especially if it will delay leukaemia treatment.[23] In our study, the mortality rate was 76.5% during hospitalization, and 30th day mortality rate was 64.7% in 34 patients. These higher mortality rates than in the literature may be due to higher median age and more patients receiving concomitant therapy when we compared the groups who received concomitant cytoreduction drug or chemotherapy with leukapheresis or did not, the decline of leukocyte count, the efficiency of leukapheresis and the rate of mortality were found no difference between groups.

CONCLUSIONS

Hyperleukocytosis is a haematological emergency which should be diagnosed and treated without delay. Leukapheresis is also one of the treatment options, and there are evidence-based recommendations regarding the initiation, discontinuation and technical application of leukapheresis in ASFA guidelines.[20] Also, the European Leukemia Net suggests leukapheresis could be applied with chemotherapy in AML patients with leukostasis.[34] There is no clear standardization of performing leukapheresis in leukaemia patients; it may depend on the centre and clinician's choice and availability of technical support. Our study concluded that concomitant cytoreductive treatment with leukapheresis did not abolish the high early death rate in leukaemia patients with hyperleukocytosis.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Trakya University Medical Faculty Hospital. (Decision number: 02/08, date: 13.02.2023).

Authors' Contribution

Study Conception: TAK, AMD; Study Design: TAK, AMD; Supervision: TAK, AMD; Fundins: TAK; Materials: TAK; Data Collection and/or Processing: TAK; Analysis and/or Data Interpretation: TAK; Literature Review: TAK; Critical Review: TAK; Manuscript preparing: TAK.

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