The effect of therapeutic leukapheresis on early complications and outcomes in patients with acute leukemia and hyperleukocytosis: a propensity score-matched study

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BACKGROUND: Hyperleukocytosis in acute leukemia is associated with higher early mortality due to the major complications of leukostasis, tumor lysis syndrome (TLS), and disseminated intravascular coagulopathy (DIC). Leukapheresis remains an important modality for the management of patients with acute leukemia and hyperleukocytosis. However, the role of leukapheresis in early mortality is controversial. This study sought to evaluate the prognostic impact of leukapheresis and its beneficial effects on TLS and DIC.

STUDY DESIGN AND METHODS: We conducted a propensity score-matched study of 166 patients with acute leukemia and hyperleukocytosis admitted between 2006 and 2016. The incidence of TLS and DIC was determined using well-defined Cairo-Bishop criteria for TLS and International Society of Thrombosis and Haemostasis criteria for DIC.

RESULTS: Before matching, 27 of 91 patients (30%) with acute myeloid leukemia (AML) and 32 of 75 patients (43%) with acute lymphoblastic leukemia (ALL) underwent leukapheresis. Propensity score matching was performed to adjust for clinical disparities between the leukapheresis and without-leukapheresis groups and resulted in 22 matched pairs of patients with AML and 16 matched pairs of patients with ALL. After matching, we observed no significant difference in early mortality rates or in the incidence of TLS or DIC between the two groups of patients with AML and ALL.

CONCLUSION: Although leukapheresis may rapidly reduce white blood cell counts and leukemic blasts, any positive influence of leukapheresis could not be demonstrated by an effect on survival outcome and the incidence of early complications, such as TLS and DIC. These results suggest that a routinely performed, prophylactic leukapheresis cannot be recommended.

Hyperleukocytosis is usually defined as a white blood cell (WBC) count greater than 100 × 10^9/L, and the reported incidence of hyperleukocytosis is between 5 and 20% in acute myeloid leukemia (AML) and between 10 and 30% in acute lymphoblastic leukemia (ALL).[1-3] Hyperleukocytosis is associated with increased early morbidity and mortality because of several complications, including leukostasis associated with tissue hypoxia, tumor lysis syndrome (TLS), and disseminated intravascular coagulopathy (DIC).[3]

Because leukemic blasts are larger and less deformable than mature WBCs and red blood cells (RBCs), leukostasis with tissue hypoxia has been explained by a rheological model of increased viscosity.[4,5] Another proposed mechanism for its pathogenesis includes interactions between leukemic blasts and the endothelium or the activation of endothelial cells by leukemic blast-secreted

ABBREVIATIONS: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; DIC = disseminated intravascular coagulopathy; ISTH = International Society of Thrombosis and Haemostasis; LGS = leukostasis grading score; PS = propensity score; TLS = tumor lysis syndrome.

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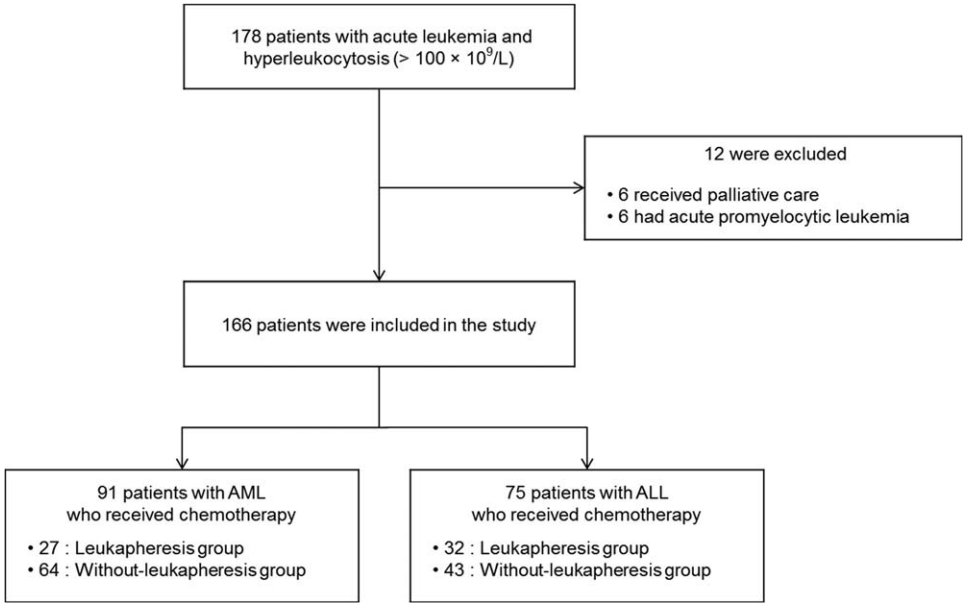

Fig. 1. Flow algorithm for patient selection and analysis.

cytokines.[2,6-8] Clinically, leukostasis could be diagnosed by characteristic respiratory or neurologic symptoms in patients with acute leukemia and hyperleukocytosis. However, the clinical and radiographic manifestations of leukostasis are difficult to distinguish from other complications of acute leukemia.[2,6]

TLS is characterized by hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia as a result of spontaneous or treatment-induced leukemic blast destruction.[9,10] Such complications can lead to acute renal failure, cardiac arrhythmia, seizures, and sudden death. Also, DIC could develop as a result of systemic intravascular activation of coagulation due to the rapid release of tissue factor from leukemic blasts.[3] Both TLS and DIC could be diagnosed in an objective manner using the Cairo-Bishop criteria for TLS and the International Society of Thrombosis and Haemostasis (ISTH) criteria for DIC.[11,12]

Therapeutic leukapheresis has been used for rapid leukoreduction in patients with acute leukemia and hyperleukocytosis. The goal of this procedure is to decrease the acute symptoms of leukostasis, prevent the development of leukostasis, and reduce the severity of TLS and DIC.[3,13,14] Moreover, leukapheresis could help mobilize leukemic blasts in the S phase to improve the sensitivity of cell cycle-dependent chemotherapy.[15] Although leukapheresis is a very efficient procedure for decreasing the number of circulating WBCs, the effects on early mortality have been heterogeneous in previous reports.[16-19]

The aim of this study was to investigate the characteristics and clinical outcomes of patients with acute leukemia and hyperleukocytosis. Furthermore, we report the results from a propensity score (PS)-matched analysis for evaluating the efficacy of leukapheresis on early mortality and complications, including TLS and DIC.

MATERIALS AND METHODS

Patients

Between January 2006 and January 2016, 178 patients who were diagnosed with acute leukemia with an initial WBC count greater than 100×10^9/L were retrospectively identified using a centralized electronic data repository at our institution. Six patients with acute promyelocytic leukemia were excluded, because treatment options and prognosis for acute promyelocytic leukemia are distinctly different from other subtypes of AML.[2] Six patients who were managed palliatively were also excluded. In total, 166 patients who received chemotherapy combined with leukapheresis or chemotherapy alone were included in this study (Fig. 1).

Baseline characteristics at presentation including age, gender, diagnosis, and symptoms/signs related to leukostasis, were analyzed. We applied a leukostasis grading score (LGS) to enrolled patients to determine the severity of leukostasis. This LGS was developed by Novotny and colleagues to identify the clinical probability of leukostasis,[20] and Piccirillo and coworkers demonstrated good correlation between the LGS and early death.[21]

The following laboratory data from the first week of admission were analyzed: complete blood counts; coagulation studies including prothrombin time, D-dimer, and fibrinogen; and routine blood chemistry, including electrolyte, lactate dehydrogenase (LDH), uric acid, phosphorus, and corrected calcium. Additional data were

obtained on the records of cytoreductive chemotherapy and leukapheresis, early mortality rate within 2 weeks, and total mortality rates. This retrospective study was approved by the Institutional Review Board at Severance Hospital, which is affiliated with Yonsei University Health System.

Leukapheresis

All leukapheresis procedures were performed according to the institutional standard operating procedures after informed consent. Leukapheresis was performed with a continuous-flow blood cell separator (COBE Spectra; TerumoBCT, software version 7.0) via central venous access. On average, two blood volumes were processed in each leukapheresis session. Anticoagulant citrate-dextrose solution A was used as an anticoagulant at a ratio of 1 to 12 for adults (body weight $\geq$30 kg) and for children (body weight $<$30 kg) at a ratio of 1 to 15 without RBC sedimentation agents. The priming of the extracorporeal line with irradiated RBCs was used for patients who had a body weight below 30 kg, but the decision was made on a case-by-case basis, according to the patient's condition. The leukapheresis procedures were continued on a daily basis until clinical improvement was determined by the physician in consultation with the director of the blood bank.

Definition of TLS and DIC

According to the Cairo-Bishop definition, laboratory TLS is defined as any two or more of the following laboratory abnormalities occurring within 3 days before or 1 week after the initiation of therapy: uric acid ($>$8 mg/dL), potassium ($>$6 mmol/L), phosphorus ($>$6.5 mg/dL for pediatrics, $>$4.5 mg/dL for adults), or corrected calcium ($<$7 mg/dL). Clinical TLS was defined as laboratory TLS accompanying one or more of the following: increased serum creatinine level ($\geq$1.5 times the upper limit of the age-appropriate normal range), history of acute kidney injury, cardiac arrhythmia, seizure, and sudden death.[11]

The ISTH criteria for DIC were used for diagnosing overt DIC. This score included laboratory values of platelet counts, prothrombin time, D-dimer, and fibrinogen. If the total score was 5 or greater, then it was compatible with "overt DIC"; if it was less than 5, then it was suggestive of "non-overt DIC"; and if it was 0, then it was "not overt DIC."[12,22]

PS-matched analysis

Before performing PS matching, we conducted univariate and multivariate analyses of all potentially available factors related to the selection of leukapheresis treatment.[23,24] Three variables, including age ($p < 0.001$), initial WBC count ($p < 0.001$), and the presence of leukostasis symptoms ($p = 0.005$), were identified and were significantly associated with the selection of leukapheresis treatment. A PS for the predicted probability of receiving leukapheresis for each patient was estimated by a logistic regression model that fit the three factors. Then, we performed a PS-matched analysis by attempting to match each patient who received leukapheresis with those who did not receive leukapheresis (a 1:1 match). Using the nearest-neighbor–matching method, we matched patients based on their diagnosis (AML or ALL) and their PS. A match occurred when the difference in logits of PS was less than 0.2 times the standard deviation of scores.

Statistical analysis

Descriptive statistics are presented as medians and interquartile ranges (IQRs) for continuous variables or as numbers and percentages for categorical variables. Comparisons between groups were analyzed using the Mann-Whitney U test for continuous variables and the exact test for categorical variables. The distributions of continuous variables and categorical variables between the leukapheresis and without-leukapheresis groups in the matched data were compared with the McNemar test and paired t tests, respectively. Survival was analyzed with the Kaplan-Meier method, and differences between groups were qualified with log-rank testing. All reported p values were two-sided, and significance was assumed if p was less than 0.05. Statistical analyses were performed using R statistical software (version 0.99.893-2009-2016; R Studio, Inc.).

RESULTS

Baseline characteristics before PS matching

Demographic and clinical variables of the data set before and after PS matching are summarized in Tables 1 and 2, respectively. Twenty-seven of 91 patients (30%) with AML and 32 of 75 patients (43%) with ALL who had hyperleukocytosis underwent leukapheresis. The leukapheresis group was significantly younger than the without-leukapheresis group in patients with AML and in those with ALL. This was because leukapheresis was performed more frequently in pediatric patients without signs of leukostasis because of the therapeutic policy in our pediatric department. The leukapheresis group had a higher initial WBC count among patients with AML (202 vs. 138 $\times$ 10^9/L; $p = 0.001$) and patients with ALL (237 vs. 134 $\times$ 10^9/L; $p < 0.001$) than the without-leukapheresis group. LDH was higher in the leukapheresis group among patients with AML (1346 vs. 899 U/L; $p = 0.008$) than in the without-leukapheresis group, reflecting the rapid turnover of leukemic blasts.[14] However, among patients with ALL, LDH did not differ significantly in either group.

In the leukapheresis group of patients with AML, the majority of patients (85%) had clinical symptoms or signs of leukostasis, such as fatigue, dyspnea, dizziness,

TABLE 1. Baseline characteristics of patients with AML before and after PS matching

	Before matching, N = 91			After matching, N = 44		
	No. (%) or median [IQR]			No. (%) or median [IQR]		
Characteristic	Leukapheresis, n = 27	Without leukapheresis, n = 64	p value	Leukapheresis, n = 22	Without leukapheresis, n = 22	p value
Age, years	43 [18-61]	61 [44-70]	0.015	52 [24-68]	56 [34-68]	0.459
Male gender	11 (41)	32 (50)	0.399	9 (41)	13 (59)	0.366
Body surface area, m^2	3.5 [3.3-4.3]	3.8 [3.3-4.5]	0.776	3.7 [3.4-4.3]	4.1 [3.4-4.5]	0.479
Initial presenting laboratory results						
WBC count, $\times 10^9$/L	202 [148-275]	138 [116-169]	0.001	186 [149-275]	142 [121-214]	0.133
Leukemic blast, %	83 [69-92]	82 [22-94]	0.678	83 [69-92]	88 [58-93]	0.698
Hemoglobin, g/dL	7.6 [6.0-8.2]	7.4 [6.5-8.8]	0.526	7.6 [6.1-8.3]	6.8 [5.9-8.1]	0.445
Platelet count, $\times 10^9$/L	59 [38-110]	53 [31-83]	0.239	59 [37-104]	51 [29-70]	0.240
LDH, U/L	1346 [995-2264]	899 [563-1643]	0.008	1519 [1066-2474]	1202 [568-2041]	0.051
Presenting leukostasis symptoms	23 (85)	34 (53)	0.008	19 (86)	19 (86)	0.999
Fatigue	16 (59)	24 (38)		15 (68)	12 (55)	
Dyspnea	4 (15)	10 (16)		4 (18)	7 (32)	
Dizziness	4 (15)	11 (17)		3 (14)	7 (32)	
Headache	5 (19)	3 (5)		3 (14)	3 (14)	
Somnolence	2 (7)	1 (2)		2 (9)	1 (5)	
Tinnitus	0 (0)	0 (0)		0 (0)	0 (0)	
Splenic infarction	0 (0)	1 (2)		0 (0)	1 (5)	
Impaired vision	1 (4)	1 (2)		0 (0)	1 (5)	
Intracranial hemorrhage	1 (4)	1 (2)		1 (5)	1 (5)	
Leukostasis grading score						
0	4 (14.8)	30 (46.9)		3 (13.6)	3 (13.6)	
1	18 (66.7)	26 (40.6)	0.031	15 (68.2)	11 (50)	0.549
2	1 (3.7)	3 (4.7)		1 (4.5)	3 (13.6)	
3	4 (14.8)	5 (7.8)		3 (13.6)	5 (22.7)	
No. of leukapheresis procedures						
1	17 (63)			15 (68)		
2	6 (22)			6 (27)		
≥3	4 (15)			1 (5)		
Time from admission to treatments, hours						
Leukapheresis	4 [0-24]			3 [0-19]		
Chemotherapy	24 [4-45]	9 [3-40]		17 [3-34]	12 [2-41]	
Mortality						
Early mortality, ≤2 weeks	4 (15)	12 (19)	0.882	4 (18)	5 (23)	0.999
Five-year mortality	18 (67)	47 (73)	0.690	15 (68)	15 (68)	0.999

headache, somnolence, splenic infarction, impaired vision, and intracranial hemorrhage. The LGS was significantly higher in the leukapheresis group than in the without-leukapheresis group. However, in patients with ALL, no statistical difference was observed between the leukapheresis and without-leukapheresis groups with regard to the number of patients who had clinical symptoms or signs of leukostasis and the LGS.

In total, 107 leukapheresis procedures were performed, and the median number of leukapheresis procedures was 1 in patients with AML (IQR, 1-2 procedures) and 2 in those with ALL (IQR, 1-2 procedures). The most common adverse events after leukapheresis procedures was hypocalcemia (n = 10; 9.3%). Patients did not present with any severe complications, such as hypotension or cardiac arrest.

Effect of leukapheresis on survival outcomes

PS matching was employed to adjust the baseline demographics and clinical variables between the leukapheresis and without-leukapheresis groups. PS matching resulted in 22 matched pairs of patients with AML and 16 matched pairs of patients with ALL. After matching, baseline characteristics of both groups among patients with AML and those with ALL were well balanced (Tables 1 and 2).

Before PS matching, the early mortality rate (defined as mortality within 2 weeks of presentation) did not differ statistically between the groups that did and did not receive leukapheresis among patients with either AML (15 vs. 19%; p = 0.882) or ALL (0 vs. 5%; p = 0.609), and the same was true for the 5-year mortality rate (AML, p = 0.690; ALL, p = 0.999). Similarly, after PS matching, the early mortality rate did not differ statistically between the leukapheresis and without-leukapheresis groups among patients with AML (18% vs. 23%; p = 0.999); however, no early mortality was observed among patients with ALL. For the leukapheresis and without-leukapheresis groups, the 5-year mortality rate did not differ statistically among patients with either AML or ALL, nor was there any significant difference in the survival rate among patients with AML and ALL (Fig. 2).

TABLE 2. Baseline characteristics of patients with ALL before and after PS matching

	Before matching, N = 75			After matching, N = 32		
	No. (%) or mean [IQR]			No. (%) or mean [IQR]		
Characteristic	Leukapheresis, n = 32	Without leukapheresis, n = 43	p value	Leukapheresis, n = 16	Without leukapheresis, n = 16	p value
Age, years	12 [4-21]	43 [24-59]	<0.001	13 [7-60]	24 [7-30]	0.792
Male sex	20 (63)	21 (49)	0.347	11 (69)	9 (56)	0.715
Body surface area, m^2	3.2 [1.4-3.8]	4.0 [3.3-4.6]	0.006	3.3 [1.4-4.4]	4.1 [2.1-5.1]	0.227
Initial presenting laboratory results						
WBC count, $\times 10^9$/L	237 [174-354]	134 [118-191]	<0.001	189 [145-338]	170 [131-237]	0.546
Leukemic blasts, %	86 [73-93]	89 [86-94]	0.266	80 [42-88]	83 [57-90]	0.748
Hemoglobin, g/dL	7.4 [5.4-9.4]	8.3 [6.8-11.2]	0.085	7.0 [5.0-10.0]	7.6 [5.0-9.6]	0.734
Platelet count, $\times 10^9$/L	47 [30-80]	53 [24-87]	0.843	43 [30-57]	50 [26-97]	0.734
LDH, U/L	1582 [800-3533]	1151 [531-1834]	0.130	1293 [563-2376]	1239 [628-1834]	0.792
Presenting leukostasis symptoms	13 (41)	19 (44)	0.942	7 (44)	7 (44)	0.999
Fatigue	9 (28)	12 (28)		6 (27)	4 (18)	
Dyspnea	1 (3)	7 (16)		1 (5)	3 (14)	
Dizziness	3 (9)	6 (14)		1 (5)	2 (9)	
Headache	5 (16)	1 (2)		1 (5)	0 (0)	
Somnolence	0 (0)	0 (0)		0 (0)	0 (0)	
Tinnitus	0 (0)	1 (2)		0 (0)	0 (0)	
Splenic infarction	1 (3)	0 (0)		1 (5)	0 (0)	
Impaired vision	0 (0)	0 (0)		0 (0)	0 (0)	
Intracranial hemorrhage	0 (0)	0 (0)		0 (0)	0 (0)	
Leukostasis grading score						
0	19 (59.4)	24 (55.8)		9 (56.3)	9 (56.3)	
1	12 (37.5)	19 (44.2)	0.453	6 (37.5)	7 (43.8)	0.584
2	0 (0)	0 (0)		0 (0)	0 (0)	
3	1 (3.1)	0 (0)		1 (6.3)	0 (0)	
No. of leukapheresis procedures						
1	11 (34)	—		7 (44)	—	
2	14 (44)			7 (44)		
≥3	7 (22)			2 (13)		
Time from admission to treatments, hours						
Leukapheresis	5 [3-24]			8 [4-24]		
Chemotherapy	73 [25-121]	24 [3-57]		47 [24-94]	24 [4-57]	
Mortality						
Early mortality, ≤2 weeks	0 (0)	2 (5)	0.609	0 (0)	0 (0)	—
Five-year mortality	16 (50)	21 (49)	0.999	7 (44)	7 (44)	0.999

Effect of leukapheresis on TLS and DIC

Clinical and laboratory findings related to TLS and DIC before and after PS matching are summarized in Tables 3 and 4. Before PS matching, the overall incidences of laboratory TLS and clinical TLS were 8.7% (eight of 91 patients) and 5.5% (five of 91 patients), respectively, among patients with AML and 10.7% (eight of 75 patients) and 1.3% (one of 75 patients), respectively, among patients with ALL. Although uric acid levels in the leukapheresis group were higher than those in the without-leukapheresis group among patients with AML after PS matching, the incidence of laboratory TLS and clinical TLS did not differ significantly between groups.

DIC status at the first week of presentation could be analyzed retrospectively for 68% (61 of 91 patients) with AML and 59% (44 of 75 patients) with ALL. The incidence of overt DIC was not significantly different between the leukapheresis and without-leukapheresis groups (before PS matching: AML, $p = 0.196$; ALL, $p = 0.722$; after PS matching: AML, $p = 0.320$; ALL, $p = 0.620$).

DISCUSSION

A single therapeutic leukapheresis procedure can reduce the WBC count by 20 to 60%, and the primary goal of leukapheresis is to reduce the WBC count to less than 100×10^9/L.[3,13,25] Additional leukapheresis may be performed at the discretion of the attending physician, mainly based on symptoms and WBC counts. Villgran and coworkers reported that the median number of leukapheresis cycles per patient was 2 (range, 1-8 cycles) in 68 patients with AML,[26] and Berber and colleagues reported the median number of leukapheresis cycles per patient was 2 (range, 1-6 cycles) in 31 patients.[27] In our study, the first single leukapheresis procedures reduced WBC counts by 25% (from 203.4 to 152.5×10^9/L) in adult patients and by 26% (from 219.5 to 161.7×10^9/L) in pediatric patients. The median number of leukapheresis cycles was 2 (range, 1-6 cycles), and these data are consistent with those from previously published reports. In addition, the median number of leukapheresis cycles depended on the initial

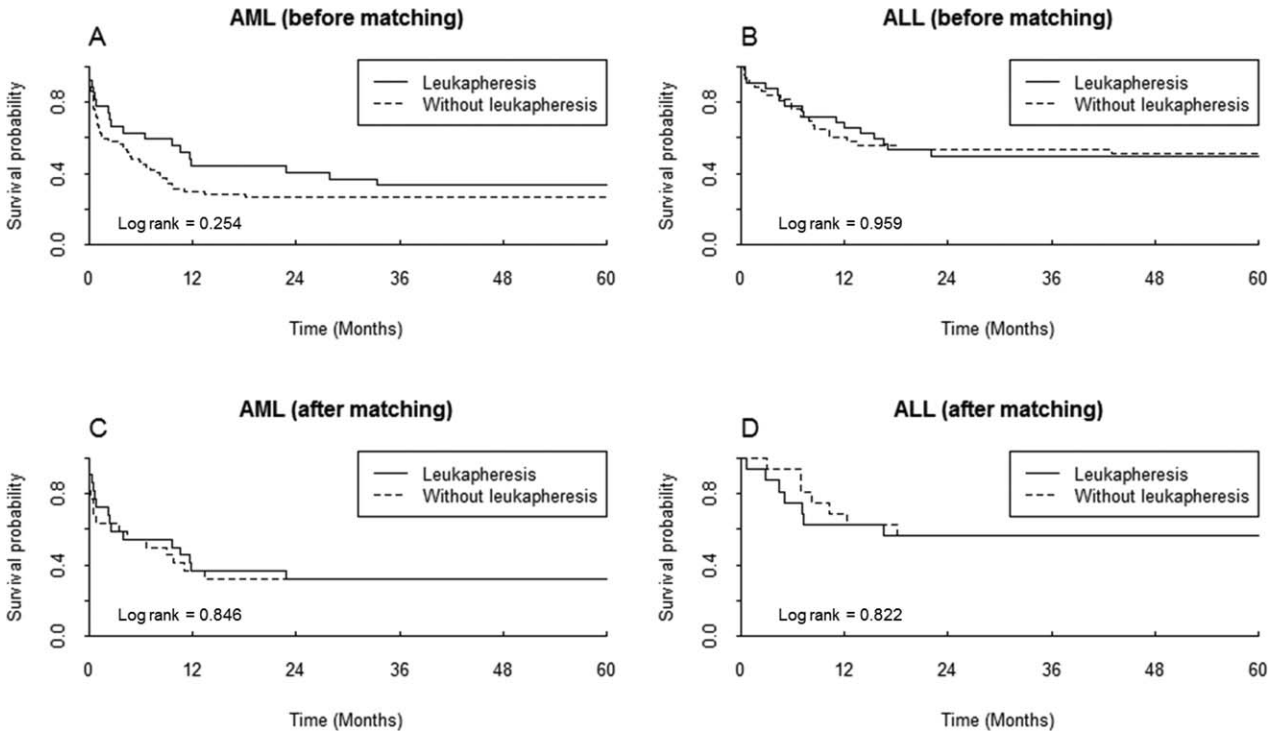

Fig. 2. Kaplan-Meier survival analysis according to leukapheresis treatment for patients with AML (A) before and (C) after PS matching and in patients with ALL (B) before and (D) after PS matching.

TABLE 3. Comparison of TLS-related and DIC-related findings between groups in patients with AML

	Before matching, N = 91			After matching, N = 44		
	No. (%) or median [IQR]			No. (%) or median [IQR]		
Characteristic	Leukapheresis, n = 27	Without-leukapheresis, n = 64	p value	Leukapheresis, n = 22	Without leukapheresis, n = 22	p value
Laboratory TLS, n (%)	2 (7)	6 (9)	0.999	2 (9)	0 (0)	0.469
Uric acid, mg/dL	5.3 [3.2-9.8]	4.8 [3.9-7.0]	0.774	7.4 [3.8-10.1]	4.8 [3.9-5.6]	0.062
Potassium, mmol/L	3.5 [2.9-4.0]	3.7 [3.2-4.1]	0.095	3.4 [2.9-4.0]	3.5 [3.2-3.9]	0.318
Phosphorus, mg/dL	3.8 [2.8-4.8]	4.2 [3.2-5.3]	0.246	3.6 [2.7-4.2]	4.3 [3.1-4.9]	0.318
Corrected calcium, mg/dL	8.6 [7.9-9.3]	8.4 [7.9-8.8]	0.326	8.7 [8.0-9.4]	8.5 [7.9-8.8]	0.173
Clinical TLS	0 (0)	5 (8)	0.322	0 (0)	0 (0)	
Creatinine, ng/mL	0.9 [0.8-1.2]	1.0 [0.7-1.4]	0.728	1.0 [0.8-1.2]	0.9 [0.7-1.2]	0.240
Acute kidney injury	6 (22)	20 (31)	0.537	6 (27)	7 (32)	0.999
Cardiac dysrhythmia	2 (7)	3 (5)	0.987	2 (9)	1 (5)	0.999
Seizure	0 (0)	1 (2)	0.999	0 (0)	0 (0)	
Sudden death	2 (7)	9 (14)	0.591	2 (9)	5 (23)	0.410
DIC score	2 [1-3]	2 [1-4]	0.757	3 [2-4]	2 [1-4]	0.942
Platelet count, $\times 10^9$/L	59 [38-110]	53 [31-83]	0.239	59 [37-104]	51 [29-70]	0.240
Prothrombin time, sec	13.4 [12.2-14.4]	13.2 [12.3-14.6]	0.917	13.4 [12.2-14.7]	12.9 [12.4-15.1]	0.970
D-dimer, ng/mL	1.5 [0.6-5.2]	3.2 [0.9-6.3]	0.255	2.0 [0.5-9.4]	3.6 [0.9-10.4]	0.368
Fibrinogen, mg/dL	256 [136-327]	330 [207-412]	0.131	283 [132-368]	346 [309-424]	0.264
DIC profile						
Overt DIC	3 (14.3)	6 (15)		3 (18.8)	4 (23.5)	
Probable not DIC	13 (61.9)	31 (77.5)	0.196	11 (68.8)	13 (76.5)	0.320
Not overt DIC	5 (23.8)	3 (7.5)		2 (12.5)	0 (0)	

WBC count, which was 1 cycle for an initial presenting WBC count less than 200 $\times$ 10^9/L and 2 cycles for an initial presenting WBC count greater than or equal to 200 $\times$ 10^9/L (data not shown).

Although a randomized, prospective study of the efficacy of leukapheresis has not yet been reported, most authors from the numerous retrospective studies have agreed that leukapheresis has no impact on long-

TABLE 4. Comparison of TLS-related and DIC-related findings between groups in patients with ALL

	Before matching, N = 75			After matching, N = 32		
	No. (%) or median [IQR]			No. (%) or median [IQR]		
Findings	Leukapheresis, n = 32	Without leukapheresis, n = 43	p value	Leukapheresis, n = 16	Without leukapheresis, n = 16	p value
Laboratory TLS	2 (6)	8 (19)	0.225	1 (6)	4 (25)	0.330
Uric acid, mg/dL	4.4 [2.6-7.9]	6.2 [3.5-8.2]	0.228	5.1 [3.6-9.8]	6.3 [3.5-7.9]	0.955
Potassium, mmol/L	3.8 [3.3-4.4]	4.2 [3.8-4.4]	0.065	3.8 [3.6-4.3]	4.1 [3.6-4.4]	0.374
Phosphorus, mg/dL	4.4 [3.6-5.3]	4.7 [3.7-5.2]	0.570	4.1 [3.5-5.0]	4.8 [4.3-5.3]	0.175
Corrected calcium, mg/dL	8.5 [8.0-8.9]	8.6 [7.9-9.0]	0.860	8.4 [8.1-9.2]	8.7 [8.2-9.1]	0.821
Clinical TLS	1 (3.1)	0 (0)	0.881	1 (6)	0 (0)	0.999
Creatinine, ng/mL	0.7 [0.5-0.8]	0.8 [0.7-1.1]	0.009	0.7 [0.5-0.9]	0.8 [0.6-1.0]	0.450
Acute kidney injury	3 (3)	1 (2)	0.410	2 (13)	0 (0)	0.456
Cardiac dysrhythmia	0 (0)	0 (0)		0 (0)	0 (0)	
Seizure	0 (0)	1 (2)	0.999	0 (0)	1 (6)	0.999
Sudden death	0 (0)	0 (0)		0 (0)	0 (0)	
DIC score	2 [1-2]	2 [1-2]	0.380	2 [2-3]	2 [1-2]	0.507
Platelet count, $\times 10^9$/L	47 [30-80]	53 [24-87]	0.843	43 [30-57]	50 [26-97]	0.734
Prothrombin time, sec	12.5 [11.6-13.4]	11.3 [11.0-12.9]	0.012	13 [11.9-13.6]	12.2 [11.1-13.1]	0.146
D-dimer, ng/mL	0.8 [0.4-3.1]	0.8 [0.4-3.0]	0.896	0.9 [0.5-2.1]	0.7 [0.3-2.4]	0.573
Fibrinogen, mg/dL	134 [86-307]	150 [53-274]	0.721	153 [109-321]	150 [94-210]	0.482
DIC profile						
Overt DIC	3 (12)	2 (10.5)		1 (9.1)	0 (0)	
Probable not DIC	20 (80)	14 (73.7)	0.722	8 (72.7)	8 (80)	0.620
Not overt DIC	2 (8)	3 (15.8)		2 (18.2)	2 (20)	

term survival.[1,3,17,28] However, the role of leukapheresis on early mortality is controversial. Several retrospective studies reported that leukapheresis could reduce early mortality in the first 2 or 3 weeks.[1,17,29] In contrast, other retrospective studies did not find an advantage in terms of early mortality, despite a significant WBC count reduction after leukapheresis.[16,28] Oberoi and colleagues performed a systematic review and meta-analysis and concluded that universal or selected use of leukapheresis or hydroxyurea/low-dose chemotherapy did not affect early mortality related to hyperleukocytosis in AML.[19]

Currently, leukapheresis is recommended as Category II (accepted as second-line therapy), Grade 1B (strong recommendation, moderate quality evidence) by the American Society for Apheresis in patients with hyperleukocytosis and symptomatic leukostasis.[25] Prophylactic, therapeutic leukapheresis could be considered as a clinical option in patients with asymptomatic hyperleukocytosis.[25,27,30,31] Thus, patients who have signs of leukostasis undergo leukapheresis more frequently according to the American Society for Apheresis guideline. Because the current situation makes it difficult to accurately analyze the clinical value of therapeutic leukapheresis in a retrospective manner, we also performed a PS-matched study to minimize the effect of selection bias and independently measure the effect of leukapheresis. Although the leukapheresis group had higher initial WBC counts among patients with AML or ALL before PS matching, which are independent risk factors of prognosis,[2] there were no statistical differences in the early and 5-year mortality rates between the leukapheresis and without-leukapheresis groups. Even after three significant variables (age, initial WBC count, and the presence of leukostasis symptoms) were controlled by PS matching analysis, both early and 5-year mortality rates showed no statistical difference between the leukapheresis and without-leukapheresis groups. Thus, our PS-matched analyses are consistent with data from the previous literature demonstrating that leukapheresis does not reduce early mortality.

Hyperleukocytosis in patients with hematologic malignancies is associated with increased morbidity and mortality because of the main complications of leukostasis, TLS, and DIC, as previously mentioned.[3] Leukostasis is pathologically defined as "the morphological evidence of intravascular accumulation of leukemic blasts occupying most or all of the vascular lumen, with or without the presence of fibrin."[32] Clinically, leukostasis is empirically diagnosed based on the symptoms of affected organs and the severity. Novotny and coworkers developed a scoring system for the probability of leukostasis based on the severity of pulmonary, neurologic, and other symptoms[20]; however, a diagnosis of leukostasis could not be made with high confidence using the scoring system because of its subjective nature.

Data analysis regarding the impact of leukapheresis on TLS and DIC has rarely been performed in previous studies. In this study, we retrospectively analyzed the incidences of TLS and DIC using the well-defined Cairo-Bishop criteria for TLS and the ISTH criteria for DIC. The incidence of TLS depends on the cancer mass, the potential for lysis of tumor cells, the underlying characteristics

of the patient, and supportive care, such as hydration and the use of allopurinol or rasburicase.[9] Dixit and colleagues reported that 130 patients (17%) developed TLS (5% clinical TLS and 12% laboratory TLS) among 772 adults with AML who received hydration and allopurinol treatment.[33] Our findings were similar (8% clinical TLS and 9% laboratory TLS) among 64 patients with AML in the without-leukapheresis group. Although the incidence of TLS in the leukapheresis group (0% clinical TLS and 7% laboratory TLS) was lower than that in the without-leukapheresis group, the difference was not statistically significant. After PS matching analysis, no difference was observed in the incidence of TLS between the leukapheresis and without-leukapheresis groups in patients with either AML or ALL. One reason for this is that most patients in both groups were effectively treated for TLS or were able to prevent it by using hydration and allopurinol. Furthermore, intravascular WBC reduction by leukapheresis is less important in preventing TLS, because most leukemic cells are located in the marrow.[2] In addition, none of the 43 pediatric patients developed clinical TLS, probably because they received urate oxidase. In pediatric patients, urate oxidase was administered to eight of 31 patients (25.8%) in the leukapheresis group and to three of 12 patients (25.0%) in the without-leukapheresis group. Urate oxidase breaks down serum uric acid and is effective in preventing and treating hyperuricemia and TLS.[34]

DIC is a pathologic process of systemic activation of the coagulation cascade and is characterized by prolonged coagulation time, thrombocytopenia, elevation of D-dimer or fibrin degradation products, and a decrease in fibrinogen. Porcu and coworkers reported a coagulopathy incidence of 30 to 40% among patients with AML and 15 to 25% among those with ALL.[28] However, the incidence of DIC developing in the early treatment period has not previously been reported based on well-defined criteria like that published by the ISTH. In our study, the incidence of "overt" DIC was 14.7% (nine of 61 patients) and 11.4% (five of 44 patients) among those with AML and ALL, respectively. Leukapheresis did not affect the incidence of DIC in patients with either AML or ALL. Considering that only 105 of 166 patients could be analyzed for DIC status in a retrospective manner, the remaining patients would not have a diagnosis of DIC, and the incidence of DIC would be lower.

In our results, leukapheresis more rapidly and efficiently reduced the WBC count compared with chemotherapy alone. However, we could not detect any positive influence of leukapheresis on either survival outcomes or the incidence of early complications like TLS and DIC. Nevertheless, our results are limited by the retrospective nature of the study and the small patient numbers. The selection of patients by the treating physician according to performance status and the presence of comorbidities or life-threatening complications that render the patient unable to tolerate leukapheresis potentially may result in selection biases and could influence the results of this study. Therefore, we cannot rule out the possibility that leukapheresis did not affect the prognosis of the patient, simply because the clinical condition of the patient who underwent leukapheresis was worse. Although it is hard to perform a well-designed clinical trial because of the rarity of this situation, a randomized prospective study is needed to better understand the impact of leukapheresis on early mortality and early complications of hyperleukocytosis. Based on our findings and previous critical reviews,[2,3,25,35,36] early initiation of induction chemotherapy with aggressive supportive care is most important for the treatment of patients who have acute leukemia with hyperleukocytosis. Routinely performed, prophylactic leukapheresis cannot be recommended, and leukapheresis can be considered in limited clinical settings of symptomatic leukostasis, such as serious respiratory failure, central nervous system involvement, and priapism.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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