

Therapeutic Leukapheresis in Patients with Leukostasis Secondary to Acute Myelogenous Leukemia

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Leukostasis is a relatively uncommon but potentially catastrophic complication of acute myelogenous leukemia (AML). Prompt leukoreduction is considered imperative to reduce the high mortality rate in this condition. Leukapheresis, usually associated with chemotherapy, is an established approach to diminish blast cell counts. We report a single center experience in managing leukostasis with leukapheresis. Fifteen patients with leukostasis of 187 patients with AML (8.02%) followed at our institution were treated with leukapheresis associated with chemotherapy. The procedures were scheduled to be performed on a daily basis until clinical improvement was achieved and WBC counts were significantly reduced. Overall and early mortalities, defined as that occurred in the first 7 days from diagnosis, were reported. A high proportion of our patients with leukostasis (46.66%) had a monocytic subtype AML (M4/M5, according to French-American-British classification). The median overall survival was 10 days, despite a significant WBC reduction after the first apheresis procedure (from $200.7 \times 10^9/L$ to $150.3 \times 10^9/L$). Almost half of patients (7/15) had an early death. Therapeutic leukapheresis, associated or not to chemotherapy, is an effective approach to reduce WBC counts in patients with AML and leukostasis; however, this therapeutic procedure does not appear to change significantly the sombre prognosis observed in the majority of patients with this complication. Other forms of treatment must be found to reduce the high mortality rate related to leukostasis. *J. Clin. Apheresis* 26:181–185, 2011. ©2011 Wiley-Liss, Inc.

Key words: leukapheresis; leukostasis; acute myeloid leukemia; hyperleukocytosis

INTRODUCTION

Hyperleukocytosis in acute myelogenous leukemia (AML) is generally defined as blast count superior to $50\text{--}100 \times 10^9/L$ in peripheral blood (PB) and has been associated with higher rates of early death (ED) and/or relapse [1–3]. Hyperleukocytosis is observed in 5–18% of adults with AML depending on the leukemia subtype, being the highest in AML with monocytic differentiation [4]. Malignant myeloid blasts adhere to the vascular endothelium, clog circulatory flow, and transmigrate into tissues [5–7]. This phenomenon results in organ dysfunction due to hypoxia, tissue infiltration, and hemorrhage, a condition called leukostasis [4,8]. Leukostasis usually compromises respiratory system, central nervous system (CNS), and renal function. Respiratory distress, possibly the single worst prognostic factor in patients with AML and hyperleukocytosis, is characterized by hypoxemia and diffuse interstitial infiltrate on chest radiograph and occurs in nearly 80% of the patients [9]. Neurological features include confusion, lethargy, stupor, headache, blurred vision, seizure, coma, papilledema, retinal vein distension, or retinal hemorrhages. This clinical condition is a rapidly pro-

gressive syndrome and fatal in the majority of patients [10].

Leukoreduction is the treatment of leukostasis, either by leukapheresis or chemotherapy. Leukapheresis is an invasive procedure that frequently requires the insertion of a central vein catheter. It is often initiated as soon as possible in patients with clinical signs of leukostasis. However, data on its impact on overall mortality and ED rate are scarce and contradictory [11,12]. In this study, we report a single center experience in treating

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patients with AML complicated by hyperleukocytosis and leukostasis. We retrospectively analyzed the clinical outcome of patients with AML with a white blood cell count of more than $50 \times 10^9/L$ and with clinical signs suggestive of leukostasis.

MATERIALS AND METHODS

Patients

We reviewed the medical chart of each of 187 consecutive adult (age over 15 years) patients with AML (excluded patients with acute promyelocytic leukemia) treated at our institution (Hospital das Clinicas de Ribeirao Preto da Universidade de Sao Paulo-USP) between January 1998 and June 2008, as previously reported [3]. Fifteen of the 187 (8.02%) were diagnosed with leukostasis and submitted to therapeutic leukapheresis (Table I). Patients with hyperleukocytosis but without signs of leukostasis were not usually submitted to leukapheresis. They were treated with conventional chemotherapy for AML.

The diagnosis and classification of AML were done based on blast cell morphology, cytochemistry, according to the French-American-British (FAB) classification [13], and immune phenotypical analysis. Cytogenetic studies were performed in a few patients only; for this reason, the karyotype results were not considered for the analyses. It was recorded the gender, age at diagnosis, white blood cell counts at presentation and daily until suspension of apheresis or death, serum creatinine, blood urea nitrogen, lactic dehydrogenase (LDH). We also evaluated clinical variables at presentation suggestive of leukostasis, such as signs of respiratory (hypoxemia, tachypnea, pulmonary infiltration on chest radiographs) and CNS involvement (defined as confusion, lethargy, stupor, blurred vision, coma, papilledema, retinal vein distension or retinal hemorrhages), renal dysfunction (blood urea nitrogen and creatinine levels), and presence of hepatomegaly and splenomegaly.

Leukapheresis

Leukapheresis procedures were initiated as soon as possible, always within 12 h from admission to hospital, and before the first course of chemotherapy. The equipment used was a continuous-flow blood cell separator COBE Spectra (Caridian BCT™, Lakewood, CO). For anticoagulation, acid citrate dextrose Formula A was added at a ratio of 1:12. We processed two blood volumes for each session, which took approximately 2–3 h. Sedimentation agents, such as hydroxyethyl starch, were not used. The collection rate was adjusted according to WBC count to optimize cell removal. The leukapheresis procedures were scheduled to be performed on daily basis until clinical improvement and/or the leukemic blast count dropped to levels below $100 \times 10^9/L$. Blood cell

TABLE I. Characteristics of Patients with AML and Leukostasis

Patient	Gender	Age	AML subtype (FAB) ^a	WBC count ($\times 10^9/L$) at admission	Creatinine (mg/dL)	LDH (U/L)	Respiratory involvement	CNS involvement	Hepatosplenomegaly	Chemotherapy (at least 2 days)	Survival (days)
1	M	51	M4	107.7	1.9	721	Yes	Yes	No	No	0
2	F	22	NC	289	1	1,859	No	Yes	No	No	1
3	M	75	M1	299	1.8	2,887	Yes	Yes	Yes	No	1
4	M	78	M4	162.3	3.2	589	No	Yes	Yes	Yes	3
5	F	45	M2	95.5	0.5	5,079	Yes	No	No	No	5
6	F	23	M2	95.1	1.7	3,347	Yes	No	Yes	Yes	5
7	M	46	M5	402	2.3	375	Yes	No	Yes	Yes	6
8	M	62	M4	104.7	1.2	1,995	Yes	Yes	No	Yes	10
9	F	64	M1	394.4	1.1	5,877	Yes	Yes	Yes	Yes	11
10	F	71	M5	271	0.7	4,347	Yes	No	Yes	Yes	15
11	F	58	M1	201	1.6	2,002	Yes	Yes	Yes	Yes	16
12	M	71	M2	142	0.8	293	No	No	Yes	Yes	30
13	M	76	M4	128.4	1.8	782	Yes	Yes	Yes	Yes	30
14	F	27	M1	118.0	0.6	322	No	No	No	Yes	273
15	M	60	M4	88	1.6	453	No	Yes	Yes	yes	417

M indicates male; F, female; AML, acute myeloid leukemia; FAB, French-American-British; NC, not categorized; WBC, white blood cell; LDH, lactic dehydrogenase; CNS, central nervous system.

^aThe diagnosis and classification of AML were done based on blast cell morphology, cytochemistry, and immune phenotypical analysis according to the FAB classification [13].

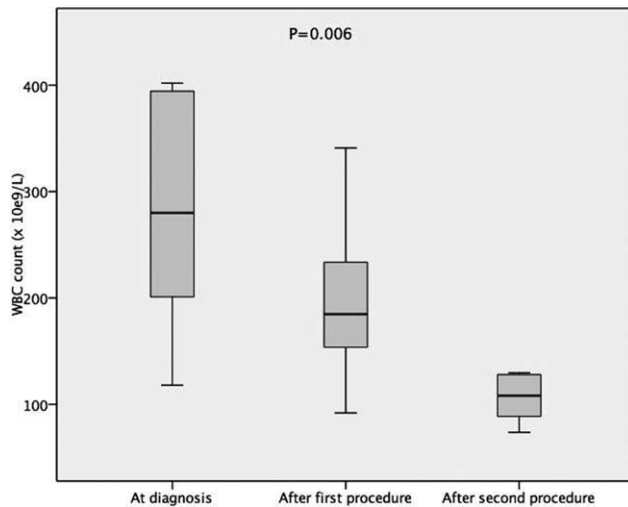


Fig. 1. White blood cell count before and after leukapheresis procedures. The mean WBC was reduced from $200.7 \times 10^9/L \pm 110.1 \times 10^9/L$ to $138.7 \times 10^9/L \pm 67.84 \times 10^9/L$ and $105.8 \times 10^9/L \pm 24.62 \times 10^9/L$, after one and two leukapheresis procedures, respectively.

counts were performed before and after the procedure. Red blood cell transfusion was avoided during the period of hyperleukocytosis to prevent the increase in blood viscosity and clinical worsening. Fresh frozen plasma and platelets concentrates were transfused whenever coagulopathy was diagnosed ($INR > 1.5$; $aPTT > 1.5$) and the platelet count was inferior to $20 \times 10^9/L$. Usually, the patients were concomitantly treated with high doses of hydroxyurea, or conventional chemotherapy with anthracycline plus cytarabine. WBC counts were reported only for the first 2 days (and leukapheresis procedure), because further WBC decrease in the following days could have been influenced by the concomitant chemotherapy.

Statistical Methods

SPSS 11.5 (SPSS, Chicago, IL) was used for statistical tests. Descriptive analyses were carried out for all variables, and their means were checked by Shapiro-Wilk test to evaluate the Gaussian distribution. Comparison of categorical variables (clinical features or events) was performed using Fisher's exact test. Continuous variables were compared using unpaired nonparametric test (Mann-Whitney). Data with non-Gaussian distribution were shown as median and range. For the whole analysis, statistical significance was assumed if $P < 0.05$.

This study was approved by our institution Ethics Committee (number 8736/2008).

RESULTS

Fifteen patients with leukostasis of 187 patients with AML (8.02%) were submitted to a median of 2 (1–3) procedures of leukapheresis to reduce their blood cell

count (for patients' characteristics, see Table I). The absolute peripheral WBC, given as mean, was $200.7 \times 10^9/L \pm 110.1 \times 10^9/L$ at diagnosis, reduced to $150.3 \times 10^9/L \pm 86.5 \times 10^9/L$ after the first leukapheresis procedure ($P = 0.035$). Six patients were submitted to a second procedure. WBC count decreased from $279.2 \times 10^9/L \pm 110.1 \times 10^9/L$ to $198.3 \times 10^9/L \pm 84.6 \times 10^9/L$ (first procedure) and to $105.9 \times 10^9/L \pm 24.4 \times 10^9/L$ (second procedure; $P = 0.006$; Fig. 1). Only one patient was submitted to third procedure with further WBC reduction (data not shown). Patients did not present any severe complication that could be attributed to apheresis procedures.

Seven of 15 patients (46.66%) with leukostasis had a monocytic subtype AML according to FAB classification, whereas 31 of 172 patients (18.02%) without leukostasis had this subtype ($P = 0.0154$) [3].

Analysis of Mortality

The median overall survival (OS) of the 15 patients with hyperleukocytosis and clinical signs of leukostasis was 10 days (range 0–417), whereas the OS of patients without hyperleukocytosis and without leukostasis was 150 days (range 1–2,627; $P < 0.0001$), as shown previously by Oliveira et al. [3]. Seven of 15 patients (46.66%) died within 7 days from diagnosis, defined as ED. There were no statistical differences between the ED group and the group of patients that survived more than 7 days regarding age, gender, WBC count, LDH, serum creatinine, FAB classification, respiratory and CNS involvement, hepatosplenomegaly, and coagulation tests (Table II).

DISCUSSION

Hyperleukocytosis is associated with a high rate of ED in patients with AML, especially when accompanied by clinical evidence of leukostasis, such as neurologic symptoms and respiratory distress [11]. Approximately 8% of our adult patients with AML presented hyperleukocytosis and clinical signs of leukostasis, a result similar to that obtained by Marbello et al. [14]. These authors reported 45 patients with AML and hyperleukocytosis ($>100,000 \times 10^9 L^{-1}$) from a total of 245 patients with AML. Sixteen of them were diagnosed with leukostasis, which means 6.53% of all their patients with AML. These studies, including ours, suggest that somewhat less than 10% of patients with AML present leukostasis. Others have shown comparable figures, however, most of them have reported the percentage of patients with hyperleukocytosis rather than with leukostasis [15,16].

Clinical leukostasis was defined as the presence of hyperleukocytosis and compromise of at least one of the following: respiratory system, CNS, or renal failure. Two-thirds of our patients had respiratory involvement

TABLE II. Comparison of Parameters According to Survival

	Survival \leq 7 days (early death) ($n = 7$)	Survival $>$ 7 days ($n = 8$)	<i>P</i>
Median age (years)	46	63	0.281
Gender (M/F)	4/3	4/4	0.595
WBC count ($\times 10^9/L$) (Mean \pm SD)	207.23 \pm 122.49	180.94 \pm 104.72	0.779
Median creatinine (mg/dL)	1.8	1.15	0.121
Median LDH (U/L)	1,859	1388.5	0.779
M4/M5 of FAB classification (%)	3 (50) ^a	4 (50)	0.704
Respiratory involvement (%)	5 (71.4)	5 (62.5)	0.573
CNS involvement (%)	4 (57.1)	5 (62.5)	0.622
Hepatosplenomegaly (%)	4 (57.1)	6 (75)	0.427
INR and/or aPTT ratio $>$ 1.5 (%) ^b	4 (66.7)	3(60)	0.750

M indicates male; F, female; WBC, white blood cell; SD, standard deviation; M4/M5, subtypes of acute myeloid leukemia according to French-American-British (FAB) classification; LDH, lactic dehydrogenase; CNS, central nervous system; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

^aThis variable was analyzed in only six patients in this group, because we could not define the FAB classification in one of them.

^bThese variables were analyzed in 6 and 5 patients.

and more than half of them presented CNS alteration. Furthermore, the median value of serum creatinine was elevated (1.6 mg/dL), indicating some degree of renal failure. Also, half the patients with leukostasis had a monocytic (M4/M5) subtype of AML, which is a higher percentage than that observed in our patients with AML without leukostasis (18.02%; 31/172). This finding is in accordance with previous studies [15,17].

Therapeutic leukapheresis is considered as the mainstay for the treatment of hyperleukocytosis and leukostasis, largely because of its efficiency to promptly reduce the WBC counts, although its impact on outcome in patients with AML remains controversial. In this study, WBC count was reduced from $279.2 \times 10^9/L$ to $105.9 \times 10^9/L$ after two procedures. It is possible that more aggressive leukapheresis could have reduced WBC counts to lower levels than observed after two procedures; however, sometimes, even after effective removal of WBC (a high WBC count in the collected cell suspension), its circulating number remained mostly unmodified, possibly due to mobilization of blasts adhered to endothelium and from organs (bone marrow, spleen). One study has shown that leukapheresis improved cerebral hemodynamics in the setting of an elevated WBC count and symptoms of CNS leukostasis in a patient with AML [18]. Others have demonstrated that leukapheresis had a role in reducing early mortality in patients with hyperleukocytic AML [15,19]. However, these studies were not randomized, and the data were obtained from relatively small cohorts of patients. In contrast, Porcu et al. have not demonstrated the benefits of leukapheresis in patients with hyperleukocytic AML despite the efficient blast reduction [11]. It seems that there is “a point of no return” in leukostasis, beyond which even rapid WBC reduction would be ineffective. However, it is difficult, or impossible, to define with exactitude this point in a specific patient. In the light of the literature on this

issue and the urgency for WBC reduction, the American Society of Apheresis (ASFA) recommends leukapheresis for leukostasis (category I) [20].

In this study, we observed that the median survival of our patients with leukostasis was only 10 days (0–417), a shorter survival than previously reported by our group to the general population of patients with AML [3]. Almost half of the patients (7/15) had ED. Furthermore, we did not identify any particular characteristics, such as age, gender, respiratory and CNS involvement, hepatosplenomegaly, WBC count at admission, serum creatinine, LDH, or coagulopathy, in this group of patients to distinguish it from the group that presented lower early mortality. These disappointing results confirm that leukostasis is a catastrophic clinical condition, most frequently irreversible despite efficient leukoreduction by leukapheresis and/or chemotherapy, which is not in accordance with findings obtained by others [19].

CONCLUSIONS

There has been small improvement (or none at all) in the mortality rate of AML patients with leukostasis, despite the prompt and aggressive treatment with apheresis and/or chemotherapy and improved supportive care. Patients with monocytic-type AML are at a particular high risk to develop leukostasis. Findings from our institution and from others suggest that therapeutic leukapheresis could benefit some patients (perhaps the few who survived beyond 15 days) with clinical leukostasis. For this reason, we recommend the performance of leukapheresis as soon as possible for all patients with leukostasis. Nevertheless, we believe it is imperative to develop alternative therapeutic approaches for this condition.

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