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Effect of leukapheresis on blood coagulation in patients with hyperleukocytic acute myeloid leukemia

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ABSTRACT

Introduction: Leukapheresis has been proposed to reduce white blood cell (WBC) count in hyperleukocytic acute myeloid leukemia (AML). However, no survival benefit has been proven and leukapheresis can potentially affect coagulation and worsen bleeding and disseminated intravascular coagulation (DIC). We analyzed the effect of leukapheresis on coagulation tests in a cohort of hyperleukocytic AML patients.
Methods: Retrospective chart review of hyperleukocytic AML patients who underwent leukapheresis between 2003 and 2014. Blood coagulation tests (platelets, PT, INR, aPTT, fibrinogen, D-Dimers and fibrin degradation products (FDP)) were collected before and after each procedure and DIC score was computed. Transfusions of platelets and coagulation factors were collected.
Results: Ninety patients and 129 leukapheresis sessions were screened. After exclusion of the sessions associated with transfusions, we observed in 44 patients a significant decrease in platelets (from 75.69 ± 89.48 to $44.59 \pm 47.71.10^9$/L, $p = 0.001$) and fibrinogen (from 4.05 ± 1.29 to 3.35 ± 1.37 g/L, $p < 0.0005$) along with an increase in PT (from 14.62 ± 2.73 to 15.62 ± 3.63 s, $p = 0.001$), aPTT (from 33.70 ± 6.32 to 39.24 ± 13.53 s, $p = 0.009$) and INR (from 1.33 ± 0.2 to 1.45 ± 0.34, $p = 0.002$) after the first procedure. Bleeding complications, all intracerebral hemorrhages, were documented in 3 patients within 24 h of leukapheresis. After combining 73 repeat procedures, we observed similar significant results except for the aPTT prolongation. The platelets and PT components of the DIC score, but not the fibrinogen component, were significantly increased after leukapheresis.
Conclusions: In hyperleukocytic AML patients, leukapheresis is associated with clinically significant decreases in platelets and fibrinogen and prolonged clotting times.

1. Introduction

In patients with newly diagnosed acute myeloid leukemia (AML), hyperleukocytosis (white blood cells count >100.10^9/L), disseminated intravascular coagulation (DIC) and bleeding complications are intricated and are associated with a high early mortality [1,2]. Leukapheresis has been proposed to quickly reduce the white blood cells (WBC) count and improve survival in patients with hyperleukocytosis and signs of leukostasis [3]. However, despite its efficiency in reducing WBC count and early reports of clinical improvement [4], its use remains controversial [2,5]. Indeed, an improvement in day 14 or day 21 survival was suggested by two retrospective cohort studies [6,7], but no difference in early mortality was observed by other authors [8,9], and recent studies failed to demonstrate an effect of leukapheresis on overall survival or respiratory status [8,10,11].

The pathogenesis of leukostasis involves mechanical vessel obstruction by blast cells as well as their increased ability to release TNF-α and IL-1β and induce their own adhesion to endothelial cells, with subsequent increased endothelial permeability and interstitial invasion [2]. Given the mechanisms involved, one would expect leukoreduction to be associated with improved outcomes. Several explanations might account for the lack of improvement though: first, the pool of leukemic cells may be quickly mobilized from the bone marrow and mitigate the reduction of circulating blasts. Second, leukapheresis may intervene too late to reverse a cascade of events already initiated. Third, leukapheresis could induce leukemic cells fragmentation and release of cellular content, including tissue factor and microparticles, which may trigger DIC. Indeed, Van Rybroek et al. reported the presence of blast cells fragments in blood after leukapheresis in a patient who developed worsening DIC, suggesting a possible role of the procedure in the patient's worsening condition [12]. Finally, leukapheresis has

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Table 1
Effect of 73 leukapheresis sessions on WBC count and blood coagulation tests in hyperleukocytic AML patients. Results are presented as mean ± SD.

	Pre-leukapheresis	Post-leukapheresis	p
WBC ($\times 10^9$/L)	154.70 ± 79.94	63.56 ± 41.13	<0.0005
Platelets ($\times 10^9$/L) (n = 67)*	65.61 ± 66.64	41.10 ± 36.27	<0.0005
Prothrombin time (s)†	15.39 ± 3.30	16.18 ± 3.64	<0.0005
Prothrombin time prolongation (s)†	2.36 ± 2.38	3.14 ± 2.82	<0.0005
INR†	1.38 ± 0.25	1.47 ± 0.30	<0.0005
Activated partial thromboplastin time (s) (n = 58)†	37.59 ± 18.28	40.16 ± 16.91	0.401
Fibrinogen (g/L) (n = 43)†	4.11 ± 1.50	3.43 ± 1.34	<0.0005

* Patients not transfused with platelets.
† Patients not transfused with coagulation factors.

been associated with a decrease in platelets count, mostly due to platelets losses during the procedure [13]; decreased fibrinogen and prolonged PT and aPTT have also been reported after leukapheresis in healthy donors [14] and cancer patients undergoing peripheral blood stem cell collection [15], and leukapheresis could therefore induce or worsen bleeding complications. The amplitude of these effects and their clinical consequences in hyperleukocytic AML patients remain unknown, but are determinant, as bleeding and thrombotic events are leading causes for early mortality in hyperleukocytic AML [16]. The objective of the present study was to assess the effects of leukapheresis on coagulation tests in a cohort of hyperleukocytic AML patients.

2. Methods

2.1. Patients and data collection

This study was approved by the Pennsylvania State University Institutional Review Board (IRB number 374). The charts of hyperleukocytic AML patients admitted to our institution between 2003 and 2014 and who underwent leukapheresis for hyperleukocytosis (WBC > 100.10^9/L) and/or signs of leukostasis were reviewed. The demographic and main clinical data, including AML subtype (myelo-monocytic or monocytic), leukostasis grading score (LGS) [17], timing of chemotherapy (including hydroxyurea), and day 28 mortality were recorded. For each leukapheresis session, coagulation tests (platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-Dimers or fibrin degradation products (FDP)) collected before and after the procedure as well as the time elapsed between those tests and the start/end of the leukapheresis were recorded. The volume of blood processed and anticoagulation used during the procedures were collected along with the transfusion of platelets, fresh frozen plasma (FFP) or administration of cryoprecipitate between the pre- and post-procedure coagulation tests. The platelets, PT, fibrinogen and FDP components of the DIC score were computed whenever possible as recommended by the International Society of Thrombosis and Hemostasis [18]. DIC was defined by a DIC score ≥ 5. Transfusions of packed red blood cells and bleeding or thrombotic complications occurring within 24 h after the leukapheresis sessions were collected.

2.2. Statistical analysis

The leukapheresis sessions associated with transfusions of platelets (between the pre- and post-procedure coagulation tests) were excluded from platelets analysis and those associated with transfusions of FFP or cryoprecipitate were excluded for analysis of PT, INR, aPTT and fibrinogen.

As part of the patients underwent several leukapheresis procedures, we performed two separate analyses: the first included all eligible leukapheresis sessions, whereas the second only included the first session for each patient, in order to avoid a selection bias due to the inclusion of several procedures for the same patients.

Results were presented as mean ± SD (SPSS, version 23). Paired *t*-tests were used to compare coagulation tests before and after procedures, and a Wilcoxon signed-rank test was used to compare the DIC score components before and after leukapheresis. We performed a Pearson's product-moment correlation test to assess the correlation between the changes in coagulation tests associated with leukapheresis and their pre-procedure levels. Unpaired *t*-tests were used to compare groups of patients. $p < 0.05$ was considered for statistical significance.

3. Results

3.1. Characteristics of the patients and leukapheresis procedures

Overall, 90 patients (54 males, 36 females, age 65.5 ± 9.1 years) and 129 leukapheresis sessions were analyzed. The WBC count was 185.21 ± 83.82.10^9/L on admission and the number of leukapheresis sessions per patient was 1 (n = 60), 2 (n = 23), 3 (n = 5) or 4 (n = 2). Day 28 mortality was 31% (28 out of 90 patients) and was not significantly associated with the number of leukapheresis sessions. Thirty-one patients had myelo-monocytic or monocytic AML. Twenty-one and 31 patients received transfusions of coagulation factors and platelets respectively during at least one of the leukapheresis sessions. All procedures used regional citrate anticoagulation and most of them involved processing of two blood volumes (1 and 3 blood volumes were processed for 5 and 3 procedures respectively). The delay between hospital admission and the first procedure was 18.0 ± 19.1 h, and none of the patients received chemotherapy before completion of all leukapheresis sessions.

3.2. Effect of leukapheresis on coagulation tests: analysis of combined procedures

Complete coagulation tests before and after procedure were available for 73 leukapheresis sessions; the delay between pre-procedure tests and leukapheresis start was 5.2 ± 4.6 h and the delay between leukapheresis end and post-procedures tests was 8.6 ± 11.6 h. The comparison of coagulation tests before and after leukapheresis (Table 1) showed a significant decrease in fibrinogen and WBC and platelets count, as well as a significant increase in PT, PT prolongation time and INR. No significant difference in aPTT was observed. There was a strong correlation between the absolute decrease in platelets and the pre-leukapheresis values ($r = 0.914$, $p < 0.0005$), and the mean reduction during the procedure was 33% of the initial values. There was a moderate correlation between changes in fibrinogen levels and pre-leukapheresis values ($r = 0.455$, $p = 0.002$) and no significant correlation was observed for PT ($r = 0.017$, $p = 0.9$).