Leukocytapheresis for the treatment of hyperleukocytosis secondary to acute leukemia

Nicole Aqui1 and Una O’Doherty1

1Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

Patients presenting with new or recurrent acute leukemia, particularly of the myeloid lineage, with WBC counts exceeding 100 × 10^9/L are often considered for leukocytapheresis, especially if they are experiencing symptoms of leukostasis. These symptoms are thought to occur because of blast aggregates and WBC thrombi in the circulation, which reduce blood flow. Leukostasis may cause various complications, including hyperviscosity syndrome, vascular occlusion resulting in intracranial hemorrhages and respiratory failure, and perivascular leukemic infiltrates. Leukostasis occurs more commonly with a high WBC count and with leukemias of monocytoid lineage such as acute myelomonocytic leukemia, which is a reflection of the nature of the leukemic blasts. Leukocytapheresis is used in an effort to quickly decrease a patient’s circulating blast count, which can both prevent the development of leukostasis and provide symptomatic relief of leukostasis. However, the impact of leukocytapheresis on early- and long-term mortality is controversial, with several studies producing conflicting results. In this chapter, the pathophysiology of leukostasis, performance of leukocytapheresis, and efficacy of this treatment are reviewed.

Learning Objective

• To gain an understanding of the pathophysiology of leukostasis and the role of leukocytapheresis as a therapeutic invention

Introduction

Leukostasis secondary to hyperleukocytosis is associated with poor survival in specific subtypes of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). Leukocytapheresis is often used prophylactically to prevent leukostasis or to improve its clinical symptoms. This chapter will provide a review of the symptoms of hyperleukocytosis, the pathophysiology of leukostasis, the technical aspects of leukocytapheresis, and the efficacy of the procedure in the treatment of complications due to leukostasis secondary to hyperleukocytosis.

Hyperleukocytosis and leukostasis

Hyperleukocytosis, defined as a WBC count >100 × 10^9/L, is a complication seen in 5%–20% of patients with acute leukemia.1,2 Risk factors include younger age, certain cytogenetic abnormalities, and monocytic differentiation subtypes (acute myelomonocytic leukemia and acute monoblastic and monocytic leukemia).2,3

Hyperleukocytosis can lead to leukostasis, tumor lysis syndrome, and disseminated intravascular coagulation (DIC). WBCs are not as deformable as RBCs, and viscosity increases logarithmically as the fractional volume of WBCs increases.4 Blast cell aggregates can cause vascular occlusion, leading to ischemic tissue injury that can result in intracranial hemorrhages and respiratory failure. In addition, leukemic blasts have a higher rate of oxygen consumption and thus may compete with tissue cells in areas of obstructed flow.4 It has also been shown that myeloblasts secrete cytokines that increase activation of endothelial cells and induce adhesion receptors on the blast cells themselves, promoting adhesion of blast cells to vascular endothelium.5

Clinical signs of leukostasis are related to the organ of injury. Pulmonary signs include tachypnea, dyspnea, and hypoxia. Nervous system symptoms include mental status changes, delirium, confusion, headache, dizziness, and tinnitus. Vascular complications are also associated with leukostasis: priapism, myocardial ischemia/infarction, and retinal hemorrhage/thrombosis.4,6,7

Patients with acute leukemia who present with hyperleukocytosis and symptoms of leukostasis have a poor prognosis, with mortality primarily due to intracranial hemorrhage and respiratory failure.8,10 This appears to be especially true with AML, in which symptoms of leukostasis can manifest in patients with WBC counts as low as 50 × 10^9/L. The incidence of leukostasis is less in chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL), perhaps in part due to the nature of the malignant cells. Unlike the typically large blasts seen in AML, CML is characterized by mature granulocytes and granulocyte precursors, whereas lymphocytes and lymphoblasts are relatively small by comparison. Symptoms are not generally observed in CML, ALL, and CLL until the WBC count is >300 × 10^9/L.6,11 Therefore, leukostasis is seen at a lower WBC count in AML than in CML and ALL, which may account for the higher incidence in AML.

Novotny et al12 have proposed a clinical grading scale to determine the risk of leukostasis in patients with hyperleukocytic leukemia. Patients were divided into 4 groups (not present, possible, probable, and highly probable) based on severity of pulmonary, neurologic, and other symptoms. Although this scale has not been widely adopted, it provides a tool to assist in the standardization of approaches to patients with hyperleukocytosis. Leukostasis remains a clinical diagnosis in which the end-organ damage is deemed likely secondary to tissue ischemia due to blast aggregates and not to other complications seen in hyperleukocytosis (eg, DIC, thrombocytopenia, or tumor lysis syndrome).

Leukocytapheresis

Apheresis is a general term that refers to the removal of a component of the blood, with the remaining components returned to
the patient. Leukocytapheresis is a procedure by which WBCs are collected and plasma, platelets, and RBCs are returned to the patient. Leukocytapheresis is used primarily in AML, but it has also been used to treat hyperleukocytosis and leukostasis associated with ALL, CML, and CLL. It is contraindicated in acute promyelocytic leukemia with translocation between chromosomes 15 and 17, where it is correlated with an increased risk of fatal or near fatal events, predominantly due to hemorrhage.13,14 Acute promyelocytic leukemia is associated with DIC and thrombocytopenia, so these patients are predisposed to bleeding complications.

Technical matters

Venous access is usually the rate-limiting step in any apheresis procedure. Peripheral access can be used, but it is recommended that a dialysis-compatible central venous catheter (CVC) be placed for several reasons: inadequate access can compromise the efficacy of the apheresis procedure, patients with acute leukemia may be unstable, and more than one procedure may be necessary.15 CVCs are placed bedside (during surgery or in the intensive care unit) or by interventional radiology.

Although leukocytapheresis can be performed via continuous or discontinuous flow blood separation, most procedures are performed using a continuous flow device such as the Cobe Spectra (Terumo BCT), which has a protocol for WBC depletion, or the newer Spectra Optia (Terumo BCT) and Fenwal Amicus, which have mononuclear cell collection protocols, but not WBC depletion protocols. The goal of leukocytapheresis is dependent on the starting WBC count and the patient’s symptoms. In general, 1.5-2 blood volumes are processed.16 A complete blood count (CBC) should be obtained before beginning the procedure, at the midway point to assess progress in reducing the WBC count and to monitor hemoglobin, and upon completion of leukocytapheresis.7,11 Additional leukocytapheresis procedures may be undertaken if clinically indicated to improve symptoms of leukostasis.16,17

Adverse reactions

Citrate (acid citrate dextrose) is the anticoagulant most commonly used to prevent clotting of the apheresis circuit. The advantage of using citrate over heparin is that it is rapidly metabolized and thus avoids prolonged anticoagulation. However, citrate binds calcium and can lead to symptoms of hypocalcemia, including tingling and numbness in the perioral area or periphery, lightheadedness, nausea, and altered taste. Very rarely, prolongations in the QTc interval may occur.15 These can be prevented or relieved by providing calcium supplementation, either oral (calcium carbonate) or intravenous (calcium gluconate). The latter is the preferable source of supplementation in the setting of leukostasis and a potentially medically unstable patient.

Blood loss is a known side effect of leukocytapheresis because contaminating RBCs are collected with WBCs.18 In patients with leukemia, who often present with severe anemia, it is even more of a concern, not only because of the expected blood loss as a result of the procedure, but also because of the extracorporeal volume (ECV). The ECV is the amount of blood outside of the body at any given time and should not exceed 15% of the total blood volume.18 The ECV varies depending on what instrument is used for the procedure, but can be as high as 285 mL (Cobe Spectra). Transfusions before leukocytapheresis are not recommended because this may worsen hyperviscosity. One option is to prime the apheresis machine with RBCs. The tubing set is first primed with normal saline, which is then displaced by RBCs through the access line. Blood priming should be considered when treating pediatric patients19 because they have a lower total body volume, as well as severely anemic adult patients. A second option is to use RBCs as part of the return fluid.

Platelet loss is a similar concern in leukemic patients undergoing leukocytapheresis. In healthy, unstimulated mononuclear cell donors, platelets can decrease by as much as 44%.20 This reinforces the importance of obtaining a postprocedure CBC to determine the need for blood product transfusions after leukocytapheresis.

Other potential side effects of leukocytapheresis are nausea, vomiting, fainting or dizziness, seizures, skin rash, hives, and flushing. There are also risks related to venous access. Whether using peripheral venipuncture or CVC, irritation, bruising, swelling, hematomas, and infection are all potential risks.

Efficacy

Despite the frequent use of leukocytapheresis in the management of acute leukemias, no randomized trials evaluating the use of leukocytapheresis in the treatment of hyperleukocytosis have been published.21 Several studies have evaluated the impact on morbidity and mortality of the use of leukocytapheresis in the treatment of acute leukemias, but have yielded conflicting results.1,17,22-25 For example, Giles et al22 published a retrospective study of 146 patients with newly diagnosed AML, of whom 71 underwent leukocytapheresis. Although the 2-week mortality rate was reduced in leukocytapheresis patients, there was no effect on long-term survival. Bug et al23 reported on 53 patients with AML and hyperleukocytosis, 25 of whom underwent leukocytapheresis. Again, although leukocytapheresis significantly lowered the risk of early death, long-term survival was similar in the 2 groups. In a study evaluating the impact of leukocytapheresis and cranial irradiation on early mortality and intracranial hemorrhage, no improvement in survival or decrease in intracranial hemorrhage was observed.17 Similarly, a German study of prophylactic leukocytapheresis in 52 patients with hyperleukocytic leukemia demonstrated no improvement in early mortality.26 A pediatric case series by Greze et al showed that leukocytapheresis can be safely performed in children with acute leukemia, but the sample size was relatively small.27 A larger pediatric study reported by the Children’s Oncology Group demonstrated no reduction in mortality with leukocytapheresis.3 Recently, Oberai et al28 performed a systematic review and meta-analysis evaluating early deaths in patients with AML and WBC ≥100 × 10⁹/L. Twenty-one studies were included, comprising 1500 adult and pediatric patients. The definition of early death varied among studies from 7 to 42 days of diagnosis or presentation. Each study was categorized based on leukocytapheresis strategy/intent to treat (universal, sometimes, or never). The most common

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<th>Indication</th>
<th>Condition</th>
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<td>Hyperleukocytosis secondary to leukemia</td>
<td>Leukostasis</td>
<td>Grade 1B</td>
<td>I</td>
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<tr>
<td>AML, WBC &gt;100 × 10⁹/L; ALL, WBC &gt;400 × 0⁹/L</td>
<td>Prophylaxis</td>
<td>Grade 2C</td>
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Table 1. ASFA guidelines for hyperleukocytosis
cause of early death was hemorrhage/bleeding (74.5%), followed by leukostasis (9.1%), sepsis (8.6%), respiratory failure (4.8%), and renal failure (2.7%). There was no difference in early mortality rate based on approach to leukocytapheresis or use of hydroxyurea and/or low-dose chemotherapy. Significant limitations exist in the included studies. All were retrospective and had moderate to high confounding bias. Oberai et al concluded that there is no demonstrated benefit to leukocytapheresis and/or hydroxyurea/low-dose chemotherapy for patients with AML and suggested that they may not have a role at all.28

According to the 2013 Guidelines on the Use of Therapeutic Apheresis in Clinical Practice published by the American Society for Apheresis (ASFA), hyperleukocytosis secondary to AML and ALL is a category I recommendation for the treatment of leukostasis and a category III recommendation for prophylaxis (Table 1).

Given the conflicting evidence of the efficacy in improving both early and long-term survival, leukocytapheresis should be viewed as adjunctive therapy to cytoreductive chemotherapy in the setting of leukostasis. Chemotherapy should be implemented as quickly as possible to prevent rapid accumulation of circulating blasts.

Is there a role for exchange transfusion/plasma exchange?

There have been a few case reports of exchange transfusion for the treatment of hyperleukocytosis in acute leukemia, predominantly in the pediatric literature. These reports describe the use of this treatment in acute leukemias presenting with extreme leukocytosis,29,30 with the achievement of a rapid reduction in circulating WBCs and a concomitant correction of the patient’s anemia with no procedure-related adverse events.

More recently, Kurnaz et al have reported a retrospective review of leukocytapheresis with and without partial plasma exchange or “volume replacement” in patients with hyperleukocytosis and leukostasis.31 They found that patients undergoing leukocytapheresis with volume replacement had significantly greater reductions in WBC counts and significantly lower early mortality compared with those who underwent leukocytapheresis alone. Although plasma cytokines were not measured, these data imply that the removal of soluble factors and/or the replacement of coagulation factors may have significant therapeutic benefit.

Conclusions

Leukostasis secondary to hyperleukocytosis is a potentially life-threatening complication of acute leukemias that carries a poor prognosis and is therefore a true emergency. Because there are no prospective, randomized studies, and retrospective studies report conflicting results, the role of leukocytapheresis for cytoreduction is still unclear. Although patients often experience symptomatic relief, there appears to be no effect on long-term survival. Therefore, it is recommended that the decision to perform leukocytapheresis should in no way delay more definitive treatment such as hydroxyurea and chemotherapy. Patients with priapism or symptoms of leukostasis should undergo leukocytapheresis as quickly as possible. In the absence of prospective trials, institutions should develop their own standardized criteria for the treatment of asymptomatic patients.

Disclosures

Conflict-of-interest disclosure: The authors declare no competing financial interests. Off-label drug use: None disclosed.

Correspondence

Nicole Aqui, MD, Department of Pathology and Laboratory Medicine, Division of Transfusion Medicine and Therapeutic Pathology, 409B Stellar Chance Laboratories, 422 Curie Blvd., Philadelphia, PA 19104; Phone: (215)746-1195; Fax: 215-662-6891; e-mail: aqui@mail.med.upenn.edu.

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