Therapeutic Apheresis in Hyperleukocytosis and Hyperviscosity Syndrome

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ABSTRACT

Therapeutic apheresis (TA), as a way of rapidly eliminating harmful or excessive blood components such as plasma proteins (plasma exchange) or cells (leukapheresis and platelet apheresis), has found broad application in a vast array of hematologic disorders. The most common hematologic indications for TA are leukocytosis in acute leukemias and hyperviscosity syndrome secondary to plasma cell dyscrasia. Leukapheresis is indicated in the initial management of leukostasis in patients with hyperleukocytosis in acute leukemias, particularly myeloid leukemias, or in patients who are at high risk of developing such a complication. Patients with lymphoid malignancies rarely develop leukostasis but may undergo cytoreduction with leukapheresis as prophylaxis for tumor lysis. The use of leukapheresis in acute promyelocytic leukemia is discouraged, given the possibility of increased risk of coagulopathy and bleeding. Similarly, therapeutic plasma exchange (TPE) represents an effective but temporary way of managing hyperviscosity syndrome secondary to immunoglobulin M paraproteins in patients with Waldenström macroglobulinemia. This review provides an overview of the pathophysiology of leukostasis and its management with leukapheresis. The use of TPE in the management of hyperviscosity syndrome is also discussed.

KEYWORDS: Hyperleukocytosis, leukostasis, acute leukemia, hyperviscosity, leukapheresis

Hyperleukocytosis, generally defined as circulating blast count exceeding 50,000 to 100,000/μL in acute leukemias, may cause impairment of organ function (e.g., respiratory failure, intracranial bleeding, or acute renal failure) and is often associated with profound metabolic abnormalities and tumor lysis. Leukostasis, primarily in the lungs and central nervous system, is a frequent complication in acute leukemia and is associated with increased early mortality in the treatment of both adults and children with the disease. As therapy for leukostasis, most physicians use urgent therapeutic leukapheresis for immediate cytoreduction in conjunction with hydroxyurea to ameliorate end-organ dysfunction, while planning for administration of cytotoxic chemotherapy. Similarly, leukapheresis is commonly used for hyperleukocytosis in the absence of leukostasis for tumor lysis prophylaxis when serious metabolic derangements are present or impending, especially in lymphoblastic leukemia with a very high white blood cell (WBC) count. However, questions regarding the use of leukapheresis for hyperleukocytosis remain, and there are no evidence-based guidelines for its use. Indeed, there are no published randomized trials of leukapheresis for hyperleukocytosis, but given that the procedure is

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generally safe, physicians are reluctant to withhold it when this complication is encountered, particularly if end-organ dysfunction is seen. It should be noted that this tenet might not apply to acute promyelocytic leukemia (APL); leukapheresis might worsen the coagulopathy and increase the rate of complications.

The first section of this review addresses the impact of hyperleukocytosis and the therapeutic value of leukapheresis in the current management of acute leukemia, focusing on AML. We describe available evidence for its benefit to patients; and explore the biologic understanding of the mechanisms of hyperleukocytosis and leukostasis.

HYPERLEUKOCYTOSIS IN ACUTE LEUKEMIAS: INCIDENCE AND CLINICAL IMPACT

Hyperleukocytosis leading to end-organ dysfunction is far more common in acute myeloid leukemia (AML) than in acute lymphoblastic leukemia (ALL). Although the WBC count may typically be higher in ALL, patients with AML are more likely to have more serious complications and organ dysfunction attributed to high WBC count.[1] In AML, ~5 to 29% of adults and a slightly higher percentage in children will present with WBC $>50{,}000/\mu L$ (WBC count is nearly entirely composed of blasts in most cases).[2–12] In a large study by the Cancer and Leukemia Group B of younger patients (age ≤ 60 years) with AML, 29% of patients had WBC $>50{,}000/\mu L$ and 12% had WBC $>100{,}000/\mu L$.[12] There are clear associations of various AML subsets with hyperleukocytosis including myelomonocytic or monocytic (FAB M4 or M5, respectively) morphology or the microgranular variant of acute promyelocytic leukemia, inv16 (p13;q22), 11q23 rearrangements, and internal tandem duplications of the *FLT3* gene (*FLT3* ITD[13]). Hyperleukocytosis is associated with adverse prognosis in APL, in part due to severe coagulopathy in these patients. Based on limited experience, leukapheresis is not recommended except as a last resort for hyperleukocytosis in APL because it may worsen the coagulopathy.[14]

Hyperleukocytosis is often seen in ALL, although clinical leukostasis is uncommon. Subsets of ALL more likely to be associated with hyperleukocytosis include ALL of T-cell phenotype and ALL associated with 11q23 rearrangements, among others. High WBC count is a clear adverse prognostic factor for overall survival in both pediatric and adult ALL,[15,16] and its presence is associated with adverse survival outcome in AML as well, especially if the WBC count is very high.[10,12] Although hyperleukocytosis does not appear to have a major impact in early mortality in ALL unless the WBC is $>250{,}000/\mu L$, in AML it is associated with increased likelihood of induction death and reduced likelihood of achieving complete remission (CR).[17–20]

CLINICAL STUDIES OF LEUKAPHERESIS FOR HYPERLEUKOCYTOSIS IN AML

The three largest studies on the role leukapheresis in the treatment of AML have come to slightly different conclusions on its efficacy. Giles et al[11] examined outcomes for AML patients with hyperleukocytosis (defined here as WBC $>50{,}000/\mu L$) in 146 patients, of whom 71 received leukapheresis. They determined that leukapheresis was associated with reduced 2-week mortality rate ($p = 0.006$) and possibly with increased CR rate ($p = 0.06$). However, there was no improvement in overall survival with the procedure; in fact, it appeared that leukapheresis was associated with worse survival. Clearly, the best explanation for this was not a deleterious effect of the procedure, but rather that the leukapheresis group was likely at higher risk, even though the authors attempted to account for this in their multivariate analysis. The multivariate analysis supported this explanation as well, given that survival benefit to leukapheresis was more evident when accounting for comorbidities and other factors.

Porcu et al[5] examined clinical features of 48 AML (or blast crisis of chronic myelogenous leukemia) patients with high WBC count ($>100{,}000/\mu L$). In this high-risk population, early death occurred in 27% of patients, in the range that others have reported for similar presentations in both adults and children.[4,7] Effective cytoreduction was not associated with improvement in survival in this trial. This is in contrast to a third study in which effective cytoreduction (defined as at least 30% reduction in WBC count) was associated with improved clinical response.[9] From that study, Cuttner et al[9] concluded that leukapheresis should be performed until the benchmark of at least 30% cytoreduction occurs. However, in the study by Porcu et al,[5] survivors did not achieve greater reductions (either percent reduction or absolute reduction) in WBC counts than nonsurvivors. Giles et al[11] also found no relationship between change in WBC count after leukapheresis and clinical outcome. Not surprisingly, it appears that the features most predictive of early death in AML with hyperleukocytosis are related to patient factors such as age, performance status, and disease complications such as coagulopathy, respiratory failure, renal failure, or neurologic compromise, rather than the degree of cytoreduction after leukapheresis, if it is used. Of note, preliminary results of a randomized study of leukapheresis versus hydroxyurea to treat hyperleukocytosis in AML were presented at the American Society of Hematology meeting in 2006. No survival benefit was shown with leukapheresis. The adverse prognosis of hyperleukocytosis for early death was again confirmed.[21]

BIOLOGIC ASPECTS OF HYPERLEUKOCYTOSIS AND LEUKOSTASIS IN AML

The underlying pathophysiology of leukostasis was described initially in autopsy studies where patients with hyperleukocytosis were noted to have organ infiltration by leukemic cells, most commonly in the lungs and brain.[22] We now know that the microvessel occlusions seen with leukostasis do not depend entirely on the high blast count alone, though clearly WBC count is a major factor. Rather, unique features of some leukemic blasts, such as activation of cell surface markers for adhesion to endothelium and cell–cell interactions, provide an explanation for why leukostasis can occur even when the blast count is $< 50{,}000$ to $100{,}000/\mu L$. The molecular mechanisms that regulate the adhesion of cells within the microvasculature or control migration of leukemic blasts into nonhematopoietic tissues are poorly understood. There is some evidence that these mechanisms may differ between subsets of leukemia. For example, Novotny et al[23] recently showed that there was a correlation between expression of CD56/NCAM (detected by immunophenotyping) and development of leukostasis in patients with myelomonocytic subtypes of AML. Using a clinical scoring system to assess risk for clinically relevant leukostasis in conjunction with flow cytometry data,[24] the authors determined that detection of CD56 expression at baseline might help to identify hyperleukocytosis patients at high risk for potentially fatal leukostasis in acute myelomonocytic leukemias (FAB M4 and M5). In a multivariate analysis, CD56 expression was the most significant predictor of leukostasis; moreover, CD56 expression also predicted worse response to leukapheresis as well.

In a fascinating study by Stucki et al,[25] it was shown that leukemic cells can promote their own adhesion to the endothelium in vitro by secreting cytokines that alter adhesion molecule activation on the endothelial cells. Several adhesion molecules such as intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin were shown to be upregulated in endothelial cells by leukemic myeloblasts, an effect regulated by blast cell production of tumor necrosis factor-α and interleukin-1β. This interesting interaction between cells creates a self-perpetuating loop in which more and more blast cells migrate and attach to the endothelium. This process highlights why rapid cytoreduction with leukapheresis and/or chemotherapy may be important to reduce early mortality. Certainly, improved understanding of the molecular mechanisms of leukostasis will be essential to target these cell–cell interactions effectively and generate better methods to predict which patients are at highest risk.

HYPERVISCOSITY SYNDROME IN HEMATOLOGIC MALIGNANCIES

The term hyperviscosity syndrome (HS) classically refers to a combination of clinical symptoms and physical findings, with laboratory documentation of an increased serum viscosity, as measured by Ostwald viscosimetry.[26] Symptoms are often related to an impairment of blood flow in the microcirculation of the central and peripheral nervous system. Symptoms associated with HS, albeit not necessarily specific to HS, include headache, dizziness, vertigo, nystagmus, hearing loss, visual impairment, somnolence, coma, and seizures. Other possible findings include mucosal hemorrhage, such as epistaxis, gingival and gastric bleeding, and congestive heart failure, the latter probably related to an expanded plasma volume.

The most common cause of HS is an increased level of plasma immunoglobulins, generally due to a plasma cell disorder.[27] In addition to the plasma concentration, the physicochemical properties of the immunoglobulin molecule are important determinants of serum viscosity, with immunoglobulin (Ig) M having the greatest effect by virtue of their large pentameric structure and heavy glycosylation, as observed in Waldenström macroglobulinemia. HS has also been described in certain cases of multiple myeloma in which abnormal polymers of IgA, IgG, or kappa light chains are produced.[28] Normal serum viscosity is between 1.4 and 1.8. centi-pose (CP)[29] Patients with values between 2 and 4 CP are only rarely symptomatic, whereas symptoms tend to occur in patients with values between 5 and 10 CP. The correlation between the concentration of the paraprotein and the resultant serum viscosity among patients is far from linear, and the risk of HS cannot predictably be inferred from the IgM level or from the serum viscosity, although in individual patients this correlation can often be established over time, once the syndrome has occurred. Some patients with Waldenström macroglobulinemia never develop HS, despite having elevated serum viscosity.

Therapeutic plasma exchange (TPE) is indicated and effective in rapidly relieving many clinical symptoms of HS in patients presenting with neurological complaints, such as headaches, tinnitus, stupor, or coma, and for those with uncontrollable or recurrent epistaxis.[30] The efficiency of TPE in eliminating plasma IgM is excellent, but IgA- or IgG-related syndromes may require a greater volume and repeat exchanges, given that a larger percentage of these smaller immunoglobulins are extravascular.[31] Most often, symptoms subside rapidly with the lowering of serum viscosity. However, irreversible changes, such as hearing loss, vestibular damage, or amaurosis, can sometimes occur despite prompt institution of TPE and rapid reduction of the serum viscosity. Finally, it should be noted that TPE is a temporary measure that does not affect the course of the

underlying disease. Thus, in the absence of other therapy, symptoms will inevitably recur.

COMPLICATIONS ASSOCIATED WITH LEUKAPHERESIS AND TPE

Although leukapheresis and TPE are performed safely in most cases, adverse reactions occasionally can be seen, and their pattern and frequency of occurrence should be well known to the practicing hematologist. As expected, adverse reactions are substantially more common when the replacement fluid is fresh frozen plasma (FFP) rather than albumin solutions. The most frequent problems are bleeding at the site of insertion of the catheter, citrate-induced hypocalcemia, muscle cramps, and FFP-related cutaneous allergic reactions manifesting as urticaria. More serious complications, such as severe anaphylactoid reactions, bronchospasm, and catheter-related or blood-borne infections are less common.

Leukapheresis generally is performed emergently in acutely ill patients with severe thrombocytopenia and coagulopathy due to acute leukemia. Thus, the placement of large-bore central venous apheresis catheters in these patients poses significant challenges, at times becoming the rate-limiting step for the initiation of this potentially life-saving procedure. Patients should be transfused aggressively with platelet concentrates and FFP before the catheters are inserted to minimize the risk of bleeding. Experienced physicians should perform the procedure. Occasionally, leukapheresis can be performed through large peripheral veins, but most patients will need a central venous access. With the proper technique and precautions, even severely thrombocytopenic patients can be accessed and undergo leukapheresis successfully.

Symptomatic hypocalcemia, with paresthesias and muscle cramps, results from the fact that the citrate anticoagulant of the blood products binds to free calcium in the patient's plasma to form soluble calcium citrate, leading to low free calcium levels. Decreasing the rate of exchange and using prophylactic calcium chloride infusions during the plasma exchange procedure can eliminate these problems or decrease their severity. Anaphylactic reactions to FFP have been reported in ~20% of patients, and are most often characterized by urticaria, fever, rigors, wheezing, and occasionally hypotension. Although most of these reactions are modest, they often represent a recurrent event that can be of significant distress to the patient and may require repeated use of corticosteroids. Very rarely TPE can result in death, usually from respiratory or cardiac complications. Anaphylaxis, vascular complications, hepatitis, sepsis, and thrombosis are other, less common causes of death.

As opposed to FFP, the use of albumin solutions for TPE will lead to a decrease in the plasma concentration of coagulation factors that may predispose to bleeding if the volume exchanged is large enough. It has been reported that after a single plasma volume exchange, for example, the prothrombin time may increase by 30% and the partial thromboplastin time may double, with a return toward normal values within a few hours.[31] More significant coagulation abnormalities are likely to be induced when multiple TPEs are performed each week or for prolonged periods of time, as is often the case when plasma exchange is used for nonhematologic applications. In patients with a preexistent risk of bleeding or in situations for which a prolonged course of TPE is planned, therefore, FFP should be used as the replacement fluid. Likewise, repeated TPE procedures with albumin solution replacement will predictably remove plasma immunoglobulins at a rate that exceeds production, eventually leading to hypogammaglobulinemia.

One of the most serious risks of TPE when FFP is used during the exchange procedure is that of blood-borne infections, particularly due to viral pathogens. Recent estimates of the prevalence rates of viral disease markers (as assessed by nucleic acid testing) among first-time blood donors in the American Red Cross pool have been reported as follows: 75.6×10^{-5} for hepatitis B virus, 299.2×10^{-5} for hepatitis C virus, 9.7×10^{-5} for human immunodeficiency virus, and 9.6×10^{-5} for human T-cell leukemia virus.[32] These estimates illustrate the current safety of the blood supply and reflect a continuous decline in the risk of transfusion-related infections in the United States. However, it should be recognized that any TPE procedure using conventional single FFP units results in the exposure of the patient to as many as 10 to 15 donors. If multiple procedures are performed over a long period of time, the cumulative exposure and resultant risk of infection are not trivial. Thus, it is essential that, when considering TPE, the treating physicians give careful consideration to the strength of the evidence supporting the indication for its use and the duration of therapy.

ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
CR	complete remission
FFP	fresh frozen plasma
HS	hyperviscosity syndrome
TPE	therapeutic plasma exchange

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