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REVIEW

Hyperleukocytosis, leukostasis and leukapheresis: Practice management

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ABSTRACT

Hyperleukocytosis, arbitrarily defined in acute leukemia as a white blood cell count greater than 100,000/mL, often is associated with increased morbidity and mortality in patients with leukemic processes. It can induce leukostasis, tumor lysis syndrome and disseminated intravascular coagulopathy and has significant prognostic implications with or without one of these clinical complications. The main sites that tend to be injured from the obstructions are the central nerve system and lungs. Despite characteristic clinical presentations, the diagnosis of leukostasis is rarely made with high confidence. The main goal of the management of hyperleukocytosis and/or leukostasis is to reduce the white blood cell count before starting induction chemotherapy. The cytoreduction can be achieved by either leukapheresis and/or hyroxyurea. The technical aspects, complications and efficacy of leukapheresis are discussed in the current article.

1. Introduction

Hypeleukocytosis is of prognostic importance in several types of leukemias. In a few situations the presence of hyperleukocytosis can even be life threatening, with or without the development of leukostasis. Leukapheresis is considered one of the common treatments for these emergent states.

The definitions, clinical manifestations, pathophysiology and therapeutic options will be reviewed. The indications, technical aspects and efficacy of leukapheresis will also be considered as well as its role in the prophylaxis and management of these emergent situations.

2. Hyperleukocytosis

Hyperleukocytosis, defined as a white blood cell (WBC) count greater than 100,000/μL, often is associated with increased morbidity and mortality in patients with leukemic processes. The number 100,000/μL is arbitrary and in every kind of leukemia the critical WBC count is different. While in patients with AML a leukocyte count of 50,000/μL can cause severe symptoms, patients with CLL can remain asymptomatic even with WBC counts greater than 500,000/μL.

In several leukemias there is an association of hyperleukocytosis with specific subtypes of the disease. For example, in AML, hyperleukocytosis has been linked, in several studies, to the monocytic differentiation subtypes (especially M4Eo, M5a)[1]; in acute promyelocytic leukemia (APL) to M3v,[2] while in ALL there is an association with t(4:11)[3] and t(9:22).[4]

The incidence of hyperleukocytosis ranges between 5% and 13% in adult AML and between 10% and 30% in ALL.[5]

Hyperleukocytosis can cause severe morbidity and mortality by inducing one or more of the following: leukostasis, tumor lysis syndrome and disseminated intravascular coagulopathy (DIC). Tumor lysis syndrome is the result of rapid cellular destruction which can induce fever and metabolic abnormalities such as hyperuricemia, hyperphosphatemia, hyperkalemia and hypocalcemia. These disturbances can lead to renal failure, cardiac arrhythmias, and death. Very high leukocyte counts typically indicate high cellular turnover and are associated with severe tumor lysis syndrome. DIC is a coagulopathy induced by the formation of small clots consuming coagulation proteins and platelets, resulting in disruption of normal coagulation and a severe bleeding tendency. One of the leading theories to explain DIC in this setting is that high leukocyte counts and cell turnover expose the circulation to very high levels of tissue factor which triggers the extrinsic pathway via Factor VII.[6]

Hyperleukocytosis has significant prognostic implications with or without one of the clinical complications mentioned above. In AML, most studies have found that hyperleukocytosis is a poor prognostic factor.[7–9] Dutcher et al.[10] showed that among AML patients, those with hyperleukocytosis had lower complete remission rate, disease free survival, and overall survival as well as a high rate of early mortality. On the other hand, Greenwood et al.[11] demonstrated that only high early mortality was affected by leukocytosis whereas other prognostic parameters were not related to the elevated WBC count.

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In ALL there are consistent data about the poor prognosis of hyperleukocytosis.[12–14] For prognostic assessment, the common arbitrary leukocyte count cut-off is 30,000/μL for B-ALL and 100,000/μL for T-ALL, although the prognostic impact of a high WBC count in B-lineage ALL is greater than in T-lineage disease.

It is unknown whether the prognostic effect of hyperleukocytosis is a result of high tumor burden or whether those leukemias with high WBC counts are distinct entities with different pathophysiology and clinical characteristics. It could be, for example, that hyperleukocytosis is an expression of a molecular change, such as the FLT3-ITD mutation in AML, and that the molecular aberration itself is responsible for the poor prognosis rather than the actual WBC count.

The management of hyperleukocytosis includes intensive supportive care and cytoreduction. Supportive care consists of prevention of tumor lysis syndrome by aggressive hydration and allopurinol, and respiratory support as needed. The cytoreduction can be achieved by leukapheresis, discussed below, induction chemotherapy and hydroxyurea. Certainly, every acute leukemia patient with hyperleukocytosis must receive induction chemotherapy. A critical problem is that if the WBC counts are not reduced prior to induction therapy, leukostasis, tumor lysis syndrome and DIC can be aggravated with the induction treatment. While leukapheresis decreases the WBC count mechanically, hydroxyurea does it chemically. There are some very old reports of hydroxyurea-induced leukocyte reduction without the development of hyperleukocytosis-associated complications in acute leukemia patients[15] and in blast crisis and accelerated phase CML patients.[16]

3. Leukostasis

Leukostasis is one of the predominant manifestations of hyperleukocytosis. The high leukocyte level leads to vascular obstruction which induces tissue hypoxia.

3.1. Clinical aspects

The central nervous system (CNS) and lungs are the most common sites for symptomatic vascular obstruction, but effects on other organ systems can occur. The CNS symptoms of vascular obstruction may include confusion, dizziness, headache, tinnitus, blurred vision, somnolence, stupor, delirium, coma and ataxia. On examination, focal deficits may be elicited, and retinal hemorrhages may be present. CT scan or MRI of the head may reveal intracranial hemorrhage. Respiratory symptoms of vascular obstruction include dyspnea, tachypnea, and hypoxemia, with the presence of auscultatory rales. A chest X-ray or a CT scan often will show bilateral interstitial or alveolar infiltrates (Fig. 1).[17] It should be noted that in patients with hyperleukocytosis, failure to immediately and properly refrigerate/place on ice a blood gas sample can result in spurious hypoxemia due to "leukocyte larceny".[18] Rare manifestations include acute leg ischemia,[19] renal vein thrombosis[20] and priapism.[21]

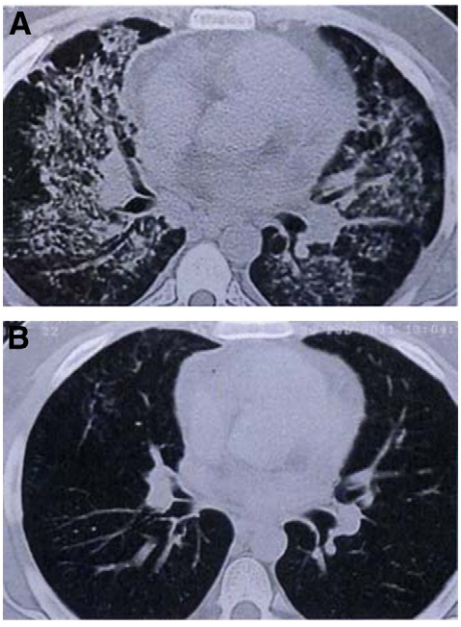

Fig. 1. A. Parenchymal infiltrates as well as diffuse ground grass opacities in a patient with monocytic AML with a white cell count of 110,000/μl. B. Clearing of pulmonary infiltrates after 3 days of leukapheresis and low-dose chemotherapy.
Reproduced with permission of the Journal of Clinical Oncology, from Piro E, et al.[50]

3.2. Diagnosis

Despite these characteristic clinical presentations, the diagnosis of leukostasis is rarely made with high confidence. In most of the cases the physician will start aggressive treatment for leukostasis when the first respiratory or neurologic symptom or sign appears in a leukemic patient with hyperleukocytosis. Pathologically, the definition of leukostasis is simpler: "the morphological evidence of intravascular accumulation of leukemic blasts occupying most or all of the vascular lumen, with or without the presence of fibrin".[22]

3.3. Diseases

In AML, leukostasis is seen most frequently in patients with WBC counts of 100,000/μL or greater. Overall, it is most common in CML, probably related to the increased frequency of hyperleukocytosis and the high corpuscular volume of the promyelocytes. In ALL, although hyperleukocytosis is frequent, leukostasis is not, and it typically occurs with higher WBC counts. Lowe and co-workers,[23] for example, showed in a large pediatric ALL series that leukostasis was most prevalent in patients with WBC counts above 400,000/μL. In CLL, this syndrome is very rare and has been described predominantly in patients with leukocyte counts above 1,000,000/μL.[24–27]

3.4. Pathophysiology

The pathophysiology of leukostasis is not clear. There are two leading theories. The rheological theory[28] relates to the principle that blood viscosity is a function of two factors, the deformability of individual cells and the volume of the cell fraction in the blood. Blasts are less deformable than mature WBCs. For elevated WBC counts, the high fractional volume of leukocytes (leukocrit) results in increased blood viscosity. As a result, the non-deformable blasts can occlude microvessels and reduce flow in the vessels with slightly larger caliber. With respect to this proposed mechanism, myeloblasts are bigger than lymphoblasts and lymphocytes, therefore leukostasis is more frequent in AML than in ALL and CLL. Hence, if it occurs in lymphatic leukemias, leukostasis does so at much higher white counts, as noted above. The other theory is based on the interaction of the blasts and the endothelium. Stucki et al.[29] demonstrated that endothelial cells activated by blasts secreted cytokines (in particular TNF-α and IL-1β), and blast–endothelial cell interaction mediated by specific adhesion receptors (i.e. selectins and VCAM-1) play a major role in promoting blast cell recruitment. Likely both mechanisms may play a role in the pathophysiology of leukostasis.[29]

3.5. Grading

Novotny et al.[30] developed a grading score for the probability of leukostasis in leukemia patients with hyperleukocytosis. This score is based on the presence or absence as well as the severity of neurologic, pulmonary and other symptoms. Patients are divided into 4

groups according to probability (none, possible, probable and highly probable) of leukostasis. An Italian group[31] retrospectively found that the 'very high probability' group had a significantly greater risk of early mortality. Different parameters suggested by other authors (e.g., age > 70 years, serum LDH > 2000 UI/L, serum total bilirubin > 1.5 mg/dL, serum creatinine > 1.2 mg/dL) were not correlated significantly (by multivariate analysis) with a high risk of early death.

3.6. Management

The principles of managing patients with leukostasis are similar to those employed for hyperleukocytosis, but it must be noted that leukostasis is a medical emergency. Efforts should be made as soon as possible to reduce the WBC counts and to support the patient. In addition to cytoreduction by leukapheresis and chemotherapy (induction and/or hydroxyurea), some centers use cranial irradiation for patients with leukostasis and neurologic symptoms[32] or even for patients with asymptomatic hyperleukocytosis.[10] There are also some anecdotal reports of successful pulmonary irradiation.[33] These treatments are controversial, and there is little evidence to support their use. With respect to the involvement of adhesion molecules in the pathophysiology of leukostasis, Porcu and colleagues[5] suggested using dexamethasone as part of the treatment. Although clinical evidence supporting its use is lacking, dexamethasone possesses the ability to inhibit upregulation of selectins and ICAMs on myeloid leukemic cells and on endothelial cells; furthermore, there is evidence that this agent can prevent hyperleukocytosis associated with ATRA treatment in APL patients.[5]

4. Leukapheresis

4.1. Definition

Apheresis stems from the Greek to take away or remove. The procedure refers to the withdrawal of whole blood from the body, separation and retention of one or more components, with the return of the remaining components to the patient. During leukapheresis, the WBCs are concentrated and removed from the blood and the other constituents are infused back into the patient.

4.2. Goals

The goal of leukapheresis is to reduce the peripheral WBC count. This maneuver can decrease the acute symptoms of leukostasis, prevent the development of leukostasis in patients with hyperleukocytosis and avoid or reduce the severity of tumor lysis syndrome and DIC.

4.3. Physiology

Although the main role of leukapheresis is to reduce the number of WBCs and blasts in the circulation, it seems that the procedure also has an influence on the marrow. Powell and associates[34] showed that leukapheresis increases the fraction of bone marrow leukemic cells that are in the S-phase. This change in the blasts, in theory, could be translated to increased efficacy of cell cycle-specific agents such as cytarabine or methotrexate.

4.4. Technical aspects

4.4.1. Continuous/discontinuous

Leukapheresis can be performed utilizing devices with either continuous or discontinuous blood withdrawal. Because of the smaller extracorporeal volume and faster procedure time, a majority of the procedures are performed utilizing a continuous flow device.

4.4.2. Volume to process

The volume to process is based upon the known efficiency of the exchange process for a component (presuming more of it is not being added during the procedure). A one blood volume exchange can remove 63% of the component, while a 2 volume exchange can remove 87%. Thus, processing two blood volumes or 10 L of whole blood, whichever is greater, should be the starting point for leukapheresis in adults. In patients who tolerate the procedure well, or when there is recruitment to the circulation from the marrow during the procedure, additional volumes can be processed.

4.4.3. Hydroxyethyl starch

Hydroxyethyl starch (HES) is a red cell sedimenting agent formerly used to improve the collection of granulocytes, bands, and metamyelocytes from normal donors. The American Society for Apheresis currently does not recommend HES for most leukocyte reduction procedures. This agent works by closely aggregating the red cells to better define the interface between red and WBCs. The use of sedimenting agents carries additional risks including volume expansion in the recipient and issues associated with use of a product whose metabolism is not well defined.

4.4.4. Citrate

Most patients will receive sodium citrate as an anticoagulant throughout the procedure. The use of citrate will decrease the patient's circulating ionized calcium concentration. Some patients may require calcium supplementation during the procedure to treat symptoms of hypocalcemia. Repletion typically is via intravenous infusion, although oral administration is an option. Calcium may be given prophylactically throughout the procedure or started when symptoms occur.

4.4.5. Product volume and its replacement

The average volume of the WBC product collected is 600 mL. Factors influencing this volume include the patient's size, the WBC count, and the volume of whole blood processed. The majority of patients undergoing leukapheresis will not require volume repletion. In those patients for whom the collection volume is greater than 15% of the blood volume, some suggest repletion with a small volume of parenteral fluids. Replacement fluid may be colloid[35] crystalloid, or blood components.[36]

4.4.6. Monitoring

The best monitors for the adequacy of leukapheresis are the patient's symptoms. Pre- and post-procedure WBC counts and leukocrits also can be helpful. An additional measure that can be used is the percent reduction in the circulating WBC mass. This value is determined by calculating the WBC count in the collection, dividing by the patient's circulating WBC mass before the procedure and multiplying by 100. A 50% decrease in the peripheral WBC count corresponds to removing 85% of the circulating WBC mass.

4.4.7. Number of procedures

A single leukapheresis procedure can reduce the peripheral WBC count by 20–50%. Most authors have reported reaching a peripheral blood count of less than 100,000/μL as the goal of leukapheresis. A majority of patients will receive a single procedure although there are occasions when patients may require additional procedures. The decision to perform additional leukaphereses procedures should be based upon the desired goal for the treatment, which traditionally is symptoms and peripheral WBC count. In a series from 6 medical centers in Taiwan, for example, 12 of 22 patients (55%) who underwent leukapheresis needed 1 procedure, 27% needed 2 procedures and only 18% needed 3 procedures.[32] When the symptoms dictate, the procedure may be performed after chemotherapy has started.

4.5. Complications

4.5.1. Hypocalcemia

Large volume leukapheresis can lead to citrate toxicity and, as a result, hypocalcemia. Treatments for this condition can include slowing the procedure, decreasing the amount of anticoagulation used, and giving the patient calcium supplements orally or intravenously, as noted above. If untreated, severe symptoms such as muscle cramps, tetany and seizures may occur.

4.5.2. Blood loss

Current devices provide users with a reliable ability to separate the WBCs from the circulating whole blood. The patient may have varying degrees of red cell or platelet loss during the procedure, most obvious when multiple procedures are performed. Decreases in hemoglobin/hematocrit will appear greater than accounted for in the product by the infusion of fluids to the patient during the procedure. Even when the red cell volume is 20% of a product, the volume of RBC loss in a 10 L procedure should be less than that in a unit of red blood cells. In patients with anemia and thrombocytopenia prior to leukapheresis, products should be given with caution prior to leukapheresis for fear of increasing the circulating blood viscosity thereby aggravating the symptoms of leukostasis. It is better to give blood transfusions, if necessary, as replacement fluid at the end of the leukapheresis procedure when the blood viscosity has been reduced.

4.5.3. Venous access

Peripheral access may be used for a leukapheresis procedure, but most prefer that a rigid wall, double lumen catheter be placed for the procedure to assure consistent flow. The large bore provides a less traumatic environment for the WBCs and decreases their mechanical destruction. When a patient is thrombocytopenic, a temporary catheter generally is inserted. Catheter-related complications, long and short term, are not unique for this procedure.

4.6. Indications

The main indication for leukapheresis is leukostasis, which is seen most frequently in CML and acute leukemia patients, especially AML. As mentioned above, some physicians also treat asymptomatic hyperleukocytosis, in order to prevent the imminent symptoms of leukostasis and attempt to reduce the severity of tumor lysis syndrome. Again, AML is the most frequent setting but it is performed as well on occasion in ALL, CML and CLL. In APL, hyperleukocytosis is associated with a unique cytokine release leading to an increased risk of early morbidity, mostly from bleeding. The level of so-called hyperleukocytes in APL, is different from other leukemias and usually refers to a level above 10,000/μl. The few available data, however, do not suggest a benefit from this modality. In fact, one group even cautioned against using apheresis in this setting.[37]

There are also some reports about patients who were treated with leukapheresis as a chronic treatment for CLL[38,39] and CML.[40] Although symptoms were reduced, the disease was not effectively treated. Leukapheresis is a unique indication for management of a new diagnosis of CML during pregnancy, in order to prevent the exposure of the fetus to cytotoxic drugs and to imatinib.[41–43]

4.7. Efficacy

While no prospective, randomized studies addressing the question of whether leukapheresis procedures benefit hyperleukocytic patients have been reported, several retrospective analyses have been published (Table 1). Giles et al.[44] reported in retrospective fashion the results of a single institution study involving 146 AML patients who had a leukocyte count above 50,000/μL; 71 subjects underwent 96 leukapheresis procedures at the discretion of the attending physician. While this intervention reduced patient mortality in the first 2 weeks ($P = 0.006$), complete remission rates and overall survival were not significantly improved. Bug et al.[45] compared two AML patient groups who had WBC counts above 100,000/μL and did ($N = 34$) or did not ($N = 28$) undergo leukapheresis; the decision to utilize this approach was based upon the treatment protocol in force at time diagnosis. While leukapheresis significantly lowers risk of early death ($P = 0.015$), there was no impact upon the attainment of complete remission or long term survival. Thiebaut et al.[46] reported a retrospective experience showing a low early death rate (2 of 53) in AML patients with a WBC count above 100,000/μL who underwent leukapheresis. The authors cautiously suggested that intervention using leukapheresis accounted for this improved result. On the other hand, Chang and co-workers[32] compared two AML patient groups who had a WBC count above 100,000/μL and did or did not undergo leukapheresis according to the decision of the attending physician. Their data showed that leukapheresis had no significant influence on early death ($P = 0.367$) or the incidence of intracranial hemorrhage. De Santis and colleagues[47] retrospectively analyzed a sub-group of 15 of 187 AML patients thought to have leukostasis and underwent leukapheresis. Despite a significant WBC count reduction after the first leukapheresis, almost half of the patients (7/15) died within the first 7 days after diagnosis. Finally, Porcu et al. and co-workers[48] reviewed their findings generated from 48 AML and CML blast crisis patients who underwent leukapheresis for a WBC count above 100,000/μL. Early deaths occurred in 27% of the patients and they found no correlation between the degree of cytoreduction by leukapheresis and early death. While some of these retrospective analyses demonstrated that leukapheresis reduces early mortality, this benefit does not result in improvement in long-term prognosis.

Table 1
Retrospective analyses describing the efficacy of leukapheresis in adult AML patients with hyperleukocytosis.

Author, year	Definition of hyperleukocytosis	Leukostasis	Number of patients		Results		
					Leukapheresis vs. no leukapheresis		
			Leukapheresis	No leukapheresis	Early mortality	CR rate	OS
Porcu 1997,[48,a]	100,000/μl	+/−	48	–	27%	NA	NA
Thiebaut 2000,[46]	100,000/μl	+/−	53	–	3.8%	55%	Median 8 months
Giles 2001,[44]	50,000/μl	NA	71	75	Decreased (P = .006)	Increased (P = .06)	Decreased (P = .06)
Tan 2005,[49]	100,000/μl	+	7	–	57%	NA	NA
Chang 2007,[32]	100,000/μl	+/−	27	37	Same	NA	Decreased
Bug 2007,[45]	100,000/μl	+/−	25	28	Decreased (P = .015)	Same	Same
Santis 2011,[47]	50–100,000/μl	+	15	–	47%	NA	NA

CR = complete response, OS = overall survival, NA = not available, Pts = patients, CML-BC = Chronic myeloid leukemia-blast crisis.
+/− = reported in some of the patients.
[a] Includes some patients with CML blast crises.

4.8. "Poor man" leukapheresis

In an emergent situation, in the absence of facilities to perform leukapheresis, judicious repeat phlebotomies with concurrent blood and/or plasma replacement, may be attempted.

4.9. Summary and recommendations

Retrospective studies consistently have shown that leukapheresis is very efficient in decreasing the number of circulating WBC. No correlation between the degree of cytoreduction and long-term patient outcome, however, has been reported. These studies are divided about the effectiveness of the procedure in reducing early death but are consistent about the ineffectiveness of the procedure in improving late prognosis. No randomized, prospective studies of the efficacy of leukapheresis have been published. The retrospective data are hampered by a lack of consistency in decisions to treat, treatments, outcomes measurements, and concomitant use of chemotherapy; therefore, conclusions are not definitive. Nonetheless, in certain rare medical conditions, such as for example, priapism, use of emergent leukapheresis is an imperative. Furthermore, there are no guidelines for uniform management of the clinical and technical aspects of this procedure. Due to the dismal prognosis and the high incidence of early mortality of patients with leukostasis, leukapheresis is commonly employed in cases of hyperleukocytosis with a high risk of leukostasis, even though a critical review of the available data suggests that in patients with hyperleukocytosis without leukostasis, early initiation of chemotherapy, hydroxyurea and supportive care are much more important than leukapheresis. If Novotny's grading system could be prospectively confirmed or other leukostasis grading systems developed and validated, these might be beneficial in determining the appropriate treatment for each setting.

Conflict of interest statement

No conflicts of interest to declare.

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