A Medical Emergency: "Leukostasis"

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Abstract: Hyperleukocytosis is commonly defined as a white blood cell (WBC) count exceeding 50-100 x 10^9 L^{-1} in peripheral blood and can be seen in newly diagnosed leukemias. Increased WBC count can lead to increased blood viscosity, leukocyte aggregation, and consequently stasis in blood vessels. Hyperleukocytic leukemia is associated with a risk of organ failure and early death secondary to leukostasis. The main sites that tend to be injured are the central nervous system (CNS) and lungs. The goal of the treatment of hyperleukocytosis and/or leukostasis is to remove leukocytes or blasts from the peripheral circulation as soon as possible and to prevent or reduce acute symptoms of leukostasis. The cytoreduction can generally be achieved by leukapheresis and/or some chemotherapeutic agents before starting induction chemotherapy. Leukapheresis is an effective and safe procedure which can be used for symptomatic relief, some special and rare conditions (serious respiratory failure, CNS involvement, priapism), or prophylactically. The supportive care has to be a part of the treatment in order to prevent tumor lysis syndrome or coagulopathy. The difference of hyperleukocytosis and leukostasis, pathophysiology and clinical presentation of leukostasis, and treatment options of hyperleukocytosis and/or leukostasis in the light of the current literature will be discussed in this review.

Keywords: Hyperleukocytosis, Leukostasis, Cytoreduction, Leukapheresis.

1. INTRODUCTION

Hyperleukocytosis can be seen in newly diagnosed acute leukemias, especially acute myeloid leukemia (AML) [1]. Some authors have demonstrated that hyperleukocytosis in AML patients is associated with higher early mortality rates [2, 3] as well as lower complete remission and long-term survival rates [2]. The presence of hyperleukocytosis is associated with severe morbidity and mortality, as a result of associated leukostasis, tumor lysis syndrome, or coagulopathy [1].

Leukostasis, a medical emergency situation, refers to hyperleukocytosis combined with organ failure. Because of its poor prognosis and the high incidence of early mortality of patients with leukostasis [4, 5], prompt and efficient therapy is needed. For this purpose either medical (hydroxyurea/low-dose chemotherapy), invasive (leukapheresis) or combined procedures should be preferred by physicians. Leukapheresis is a safe procedure [6-9] and provides a rapid and effective cytoreduction in hyperleukocytic patients with or without leukostasis [5, 7, 10-12].

The clinical sign and symptoms, pathophysiology, and finally basic treatment strategies of leukostasis will be reviewed. Evidence-based data about the experience of leukapheresis in symptomatic patients with hyperleukocytosis or its prophylactic use are also discussed extensively in the current review.

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2. HYPERLEUKOCYTOSIS

Hyperleukocytosis has been variably defined as a white blood cell (WBC) count exceeding 50 x 10^9 L^{-1} [2, 11] or 100 x 10^9 L^{-1} [12, 13]. The incidence of hyperleukocytosis is 5-13% for adult AML, while is 10-30% in acute lymphoblastic leukemia (ALL) [14]. Although hyperleukocytosis is more commonly occurred in patients with ALL than those with AML, the frequency of leukostasis is higher in AML patients compared to ALL patients. Monocytic subtypes of AML (FAB M4Eo, M5a) [15], the microgranular variant acute promyelocytic leukemia (APL-M3v) [16], t(4;11) (q21; q23) associated ALL and t(9;22) positive ALL [17, 18] has been linked with hyperleukocytosis. In contrast, some genetic abnormalities such as t(8;21), chromosome 5 and/or 7 abnormalities are associted with low WBC counts [11].

The critical threshold of WBC count for symptomatic hyperleukocytosis or leukostasis is variable in different leukemia types (Table **1**). Leukostasis is seen most frequently in chronic myeloid leukemia (CML) and AML patients. With respect to the "rheological theory", myeloblasts are bigger than lymphoblasts and lymphocytes, and therefore leukostasis is more common in myeloid malignancies than in lymphocytic ones. On the other hand, not only the quantitave or rheologic properties of circulating cells, but also the qualitative properties of these cells may be related to leukostasis development. Soares *et al*. [19] have reported 16 leukemic patients with pulmonary leukostasis and with less than 50 x 10^9 L^{-1} circulating leukocytes. The authors have suggested that

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Table 1: Critical WBC Count for The Development of Hyperleukocytosis Symptoms or Leukostasis in Different Kind of Leukemias

Disease	Subtype	Threshold WBC Count	Reference
CML		> 200 x 10^9 L^{-1}	Bruserud et al.[7]
AML			
	M4Eo	> 100 x 10^9 L^{-1}	Szczepiorkowski et al.[39]
	M5a	> 100 x 10^9 L^{-1}	Szczepiorkowski et al.[39]
	APL	> 10 x 10^9 L^{-1}	Ganzel et al.[1]
ALL		> 400 x 10^9 L^{-1}	Szczepiorkowski et al.[39]
CLL		> 1.000 x 10^9 L^{-1}	Ganzel et al.[1]

Abbreviations: WBC: White blood cell; CML: Chronic myeloid leukemia; AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia: CLL: Chronic lymphocytic leukemia**.**

pulmonary leukostasis in the absence of hyperleukocytosis may be triggered by the presence of circulating blasts or the affinity of neoplastic cells for the pulmonary endothelium. More recently, a significant association between AML cell expression of the CD11c membrane molecule and a high risk of early death in leukocytosis have been shown [12]. Furthermore, an experimental diabetic retinopathy model performed by Serra *et al*. showed that CD11b (+) bone marrow-derived monocytes expressing high levels of CCR5 were the major subset of leukocytes responsible for the pathogenesis of retinal capillary leukocytosis [20]. Both these observations [12, 19] indicate that the biological characteristics of AML cells are also seem to influence the development of leukostasis.

3. LEUKOSTASIS

"Leukostasis" is defined as hyperleukocytosis concurrent with organ dysfunction due to tissue hypoxia, tissue infiltration or coagulopathy [12]. Pathologically, the definition is as follows: "the morphological evidence of intravascular accumulation of leukemic blasts occupying most or all of the vascular lumen, with or without the presence of fibrin" [21]. With respect to this definition, the activation of the coagulation cascade is not necessarily in the pathogenesis of leukostasis.

Vascular obstruction due to sludging of high WBC count or blastic cells can lead to tissue hypoxia and eventually organ failure. The main sites tend to be affected from the leukostasis are the lungs and central nerve system (CNS) including retina [1]. Rarely, acute leg ischemia [22], renal vein thrombosis [23], priapizm [24], or splenic rupture [25] can occur.

3.1. Clinical Presentation

The clinical manifestations are reflective of the organ systems where affected by leukocyte/blast stasis and relevant tissue hypoxia. The most common symptoms/signs in a study conducted by Porcu *et al*. [13] revealed respiratory distress (39%), coagulopathy (31%), neurological symptoms (27%), and renal failure (14%). Pulmonary symptoms include tachypnea, dyspnea, and hypoxemia, with the presence of auscultatory rales and/or rhonci on physical examination. Chest imaging will reveal bilateral interstitial or alveolar infiltrates [1, 26]. The neurologic symptoms may highly range from less severe symptoms such as mild tinnitus, headache, and dizziness to severe threatening ones including delirium, intracranial hemorrhage, and coma. On physical examination, focal deficits and retinal hemorrhages may be present. The other target organs are the kidneys and heart presenting with azotemia and arrhythmia [26].

Leading symptoms of leukostasis are generally non-spesific. Furthermore, it should be kept in mind that a combination of these sign/symptoms can be detected in the same patient at presentation. For example in a newly diagnosed acute myeloid leukemia patient with symptomatic hyperleukocytosis; thrombocytopenia, intracranial hemorrhage due to low platelet counts, renal insufficieny induced by secondary tumor lysis syndrome, an impaired coagulation test profile, and additionally some neurologic symptoms such as visual abnormalities may be occurred at the same time.

3.2. Laboratory

Laboratory tests are required to confirm a clinical suspician of leukostasis. Nevertheless, hyperelevated

WBC counts may give rise to some erroneus laboratory results such as pseudothrombocytosis, pseudo-hypoxemia due to leukocyte larcency, pseudo-hyperkalemia, pseudohypoglycemia, and prolonged coagulation tests [26].

3.3. Diagnosis and Prognosis

Firstly, the clinicians must be aware of this syndrome. Despite its characteristic clinical presentation, the diagnosis of leukostasis is rarely made accurately [1]. A high clinical suspicion may lead and guide the physician to take the proper steps for making a quick and correct diagnosis. At this point, a more objective approach recommended by Novotny *et al*. [27] should be prefered. The authors developed a symptom-based grading score in order to predict the probability of leukostasis in leukemic patients with hyperleukocytosis (Table **2**). Piccirillo *et al*. [28] retrospectively showed that "very high probability" group had a significant higher risk of early mortality. Adverse prognosis was associated with age, respiratory stress, presence of coagulopathy, neurological symptoms and renal failure [13].

3.4. Pathophysiology

Despite the exact mechanism of leukostasis is not clear, there are two main hypotheses. According to the "rheological theory" [29] blood viscosity was determined by the deformability of individual cells and the volume of the cell fraction in the blood. This means that the larger (myeloblasts vs lymphoblasts/ lymphocytes) and less deformable cells (blasts vs mature WBCs) as well as higher cell counts will result in increased blood viscosity and leukostasis risk. The other leading theory, "blast-endothelial cell interaction" [30], is based on the activation of endothelial cells by the high concentration of blasts. With respect to the proposed mechanism, increased cytokine release (especially tumor necrosis factor α, interleukin 1β) [31], adhesion molecules (selectins, vascular cell adhesion molecule-1) [31], and proteolytic enzymes (matrix metalloproteases-9= MMP-9) [32], endothelial cell damage and extravasation of AML cells may contribute to blast cell recruitment. Alterations of adhesion molecule pattern in peripheral blood blasts compared with bone marrow blasts may be related with the ability of blast to circulate or leukaemisation [33]. Both mechanisms seem to play important roles in the pathophysiology of leukostasis syndrome.

As mentioned before, monocytic differentiation of AML cells has an important role in promoting hyperleukocytosis and subsequently, leukostasis. Interestingly, the nucleophosmin-1 mutation is highly associated with monocytic morphology and low expresion of the CD34 stem cell marker [34]. Similarly, MMP-9 may give rise to the tissue damage especially for AML cells with monocytic features [32, 35, 36].

3.5. Treatment Strategies

The principles of managing patients with hyperleukocytosis or leukostasis is quite similar. However, the clinican must keep in mind that leukostasis syndrome is a medical emergeny. Interventions should be started immediately. The main

Table 2: A Symptom-Based Grading Score to Predict the Probability of Leukostasis (no Obvious other Cause)[*]

Group	Probability	Severity of symptoms	Pulmonary symptoms	Neurologic symptoms	Other organ systems
0	Not present	No limitations	No symptoms and no limitations in ordinary activities	No symptoms	No symptoms
1	Possible	Slight limitations	Mild symptoms and slight limitation during ordinary activity, comfortable at rest	Mild tinnitus, headache, dizziness	Moderate fatigue
2	Probable	Marked limitations	Marked limitation in activity because of symptoms, even during less than ordinary activity, comfortable only at rest	Slight visual disturbances[**], severe tinnitus, headache, dizziness	Severe fatigue
3	Highly probable	Severe limitations	Dyspnea at rest, oxygen or respirator required	Severe visual disturbances[**] (acute inability to read), confusion, delirium, somnolance, intracranial haemorrhage	Myocardial infarction, priapism, ischemic necrosis

[*]Taken from the reference 27; [**]Blurred vision, diplopia, hemianopia

goals of the treatment is to reduce the leukemic burden and to support the patient. The cytoreduction can be achieved by either medical (low-dose chemotherapy/ hydroxyurea) or mechanical (leukapheresis) ways. At this point, no generally accepted guidelines exist. All acute leukemia patients have to receive an induction chemotherapy, and both these efforts can be termed as a "pre-therapy" which help the patient to undergo an induction chemotherapy without complication. There are also some anectodal reports of successful pulmonary irradiation [37].

With regard to its poor prognosis, some clinicians also tend to treat asymptomatic hyperleukocytosis in order to prevent the imminent symptoms of leukostasis [2].

3.6. Supportive Care

Supportive management basicly include close monitorisation of the patient, and efforts to prevent or minimize the catastrophic consequences of hyperleukostasis including tumor lysis syndrome and/or disseminated intravascular coagulation. For this purpose aggressive intravenous fluid support, allopurinol or rasburicase, and transfusion of blood components should be administered in selected cases. Redundant packed red cell transfusions should be avoided due to risk of increasing blood viscosity [26].

4. LEUKAPHERESIS

Leukapheresis refers to the withdrawal of whole blood, seperation and retention of WBCs, with the return of remaining constituents to the patient. During the procedure, the WBCs are concentrated and efficiently removed from the circulation [1]. In addition, leukapheresis increases the fraction of bone marrow leukemic cells that are in the S-phase of cell cycle [38].

A continuous flow device is commonly preferred to process a 2 volume exchange or 10 L of whole blood. A 2 volume exchange can remove 87% of the component. The average volume of the WBC product collected is 600 mL. Patient's size, the WBC count, and the volume of whole blood processed can also alter the product volume [1].

4.1. Indications

The American Society for Apheresis (ASFA) recommendations [39] for performing leukapheresis in acute leukemia patients are as follows:

1. Hyperleukocytosis with symptoms of leukostasis (grade 1B recommendation),

2. Sufficiently high WBC counts (see Table **1**) to consider prophylactic apheresis (grade 2C recommendation).

Serious respiratory failure or CNS involvement are currently regarded as indications for leukapheresis [39]. In certain rare medical emergencies, such as priapism [24, 40], leukapheresis will be an imperative treatment modality. For patients presenting with priapism, a combined modality approach including cytoreduction and local intracavernous therapy should always be considered [7, 40]. The use of leukapheresis in the setting of newly diagnosed CML during pregnancy have been reported [41-43]. Corrobation of respiratory symptom relief by therapeutic leukapheresis with physiological measurements may justify it in pregnant women with CML [44].

Nonetheless, implementation of leukapheresis in patients with APL is controversial, even some groups cautioned against using apheresis in this setting [45].

4.2. Monitoring of the Patient

As mentioned before, hyperleukocytosis is associated with an increased risk of tumor lysis syndrome and/or coagulopathy. Due to these catastrophic complications serum urea, creatinine, uric acid, potassium, calcium, phosphorus, lactate dehydrogenase levels, and at least a basal coagulation profile (prothrombin time, activated partial thromboplastin time) has to be studied by the attending physician.

The symptomatic improvement is the best way to decide the efficacy of leukapheresis. Additionally, pre- and post-apheresis WBC counts and leutokrit values, or the percent reduction in the circulating WBC mass can be beneficial for monitoring [1].

% Reduction in the Circulating WBC Mass= [WBC count in the collection / The patient's circulating WBC count before the procedure] x 100

4.3. Number of the Procedures

Daily leukapheresis should be continued until clinical improvement or reaching a WBC count of less than 100 x 10^9 L^{-1} [1, 5]. A single procedure can reduce the circulating WBC count by 20-50%. To decrease 50% of peripheral WBC count corresponds to removing

85% of the circulating WBC mass [1]. In Bruserud's series, the average number of leukapheresis for each AML patient was 2.2, and the mean WBC count reduction was 71% corresponding to a mean absolute WBC reduction of 219 x 10^9 L^{-1} [7]. Similarly in a more recent study by Berber and his colleques, the median number of procedures for hyperleukocytic AML patients was reported to be 2 per patient [1]. When there is recruitment to the circulation from the bone marrow during the procedure or when the symptoms dictate, the additional procedures may be required [1].

4.4. Complications

Leukapheresis seems to be a safe procedure both with regard to immediate complications [5-9] and effects on long-term prognosis [7]. Short-term complications include hypocalcemia associated with citrate toxicity, anemia and thrombocytopenia due to multiple procedures, and cathater-related complications. Bruserud *et al*. [7] did not observe any serious side effects during or immediately after 35 apheresis procedures performed for 16 hyperleukocytic leukemia patients. De Santis *et al*. [5] performed 21 leukapheresis procedures that begun within 12 hour after admission for 15 consecutive AML patients with the symptoms of leukostasis. Similarly, they did not report any severe side effects.

4.5. Efficacy

Although several analyses in retrospective fashion [5, 10, 11] have been published addressing the use of leukapheresis in hyperleukocytosis, no randomised, prospective studies of the efficacy of leukapheresis on early mortality or long-term prognosis are available.

The time interval for defining early deaths varied from 7 to 42 days of diagnosis or presentation [46]. Porcu *et al*. [13] reported a first-week mortality rate of 27.1% and did not find any correlation between early mortality rate and the degree of cytoreduction in 48 patients who underwent daily leukapheresis until WBC count < 100 x 10^9 L^{-1}. In a retrospective experience [10], early deaths occurred in only 3.8% of the 53 AML patients who were treated with leukapheresis, while leukapheresis was found to be ineffective in 21 patients (~40%). The early mortality rates were reported to be 57% and 47%, respectively in two smaller patient groups [4, 5] with hyperleukocytic leukemia. But it should be noted that both these studies constituted of patients with symptomatic hyperleukocytosis.

Giles *et al*. [11] compared two AML patient groups who did and did not undergo leukapheresis. Two-weeks early mortality rates, as well as long-term survival results did not differ for patients receiving apheresis or not. However, the independent predictors of survival at 2 weeks were found to be apheresis, younger age, lower WBC count and low performance status. Chang *et al*. [6] showed that leukapheresis had no significant influence on early mortality or the incidence of intracranial hemorrhage. The most significant risk factors for early death were age ≥ 65, respiratory failure, and having two or more symptoms of leukostasis. Finally Bug *et al*. [12] reviewed their findings and they emphasized that leukapheresis significantly lowers the risk of early mortality by day 21 (16% vs 32%, respectively; p= .015), while no significant difference was noted in terms of complete remission or overall survival rates. Dyspnea, elevated creatinine, higher lactate dehydrogenase serum levels were independent risk factors for early death. With respect to this benefit, the authors also remarked that leukapheresis was accepted as a standard procedure for hyperleukocytic AML patients whom admitted to their institution.

Most recently, Berber *et al*. [8] reported their results generated from 31 AML patients with hyperleukocytosis. The most common AML subtype was AML-M2. Early and total mortality rates were 16.1% and 58.1%, respectively. 14 patients experienced leukapheresis for symptomatic relief, while 17 received it prophylactically. No significant differences were noted between two groups in terms of leukapheresis effectiveness, mean survival time, early and total mortality rates. To the best of our knowledge, this is the first study, which compared leukapheresis in terms of leukapheresis indications. The same group has also compared the efficacy of leukapheresis between elderly (≥ 65 years-old; n= 18) and younger (< 65 years-old; n= 21) acute leukemia patients [9]. There were no statistically significant differences between the two groups with respect to sex, diagnosis, initial leukocyte count, lactate dehydrogenase level, number of leukapheresis procedures, rates of side effects, or early and total mortality. In addition, their cut-off WBC counts for prophylactic leukapheresis was different from ASFA's recommendations. The leukocyte counts exceeding 50 x 10^9 L^{-1} for AML M4-M5, > 100 x 10^9 L^{-1} for AML subtypes other than M3, M4, and M5, and > 200 x 10^9 L^{-1} for ALL patients were defined as thresholds for the prophylactic apheresis procedure. The latter study of the Turkish group seems to be the

first study about the effectiveness of leukapheresis in a geriatric population.

4.6. Leukapheresis or Medical Treatment for Pre-Therapy?

To decide the initial therapeutic option in a patient with symptomatic hyperleukocytosis is still controversial. A systematic review and meta-analysis [46] including 21 studies and in 1500 AML patients with hyperleukocytosis (WBC > 100 x 10^9 L^{-1}) showed that neither leukapheresis strategy (universal or selected use) nor hydroxyurea/low-dose chemotherapy influenced early deaths during first induction.

The timing of chemotherapy also varies between the studies. Concomitant therapy with a possible combined effect of leukapheresis and chemotherapy was suggested by De Santis *et al*. [5]. Some authors emphasized the importance of early, the same day as the first apheresis [11] or within 24 hours [5], cytoreductive chemotherapy. Thiebaut *et al*. [10] observed a recruitment of bone marrow cells into the S phase after the apheresis procedure. In this setting, early initiation of cell-cycle specific chemotherapeutic agents may provide additional benefits. However, a delayed chemotherapy intervention later than 48 hours after admission was significantly (p= .001) associated with increased early mortality [6].

It must be noted that the final decision about this matter of debate depends on some factors; patient characteristics, physician preferences, and the policy of the institution.

5. CONCLUSIONS

Leukapheresis offers a safe and effective treatment modality for cytoreduction in selected indications. Owing to its dismal prognosis, leukapheresis is commonly preferred in hyperleukocytic patients with a high risk of leukostasis, or some rare emergent conditions including respiratory failure, CNS involvement or priapism. In asymptomatic patients with hyperleukocytosis, pre-therapy with hydoxyurea/low-dose chemotherapy and supportive care should be prioritized rather than leukapheresis.

While some retrospective analyses demonstrated that leukapheresis reduces early mortality in hyperleukocytic leukemia patients, the effect of leukapheresis on long-term prognosis of leukemia patients is not well documented. Further randomised, prospective clinical studies on leukapheresis in the treatment of hyperleukocytosis are needed.

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