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Review

The management of hyperleukocytosis in 2017: Do we still need leukapheresis?

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ABSTRACT

Hyperleukocytosis is defined as a white blood cell count greater than 100.000/μL in patients affected by acute or chronic leukemias. Hyperleukocytosis is more common in acute leukemias than in chronic leukemias. Risk factors include younger age, acute myeloid leukemia, the microgranular variant of acute promyelocytic leukemia, acute lymphoblastic leukemia and some cytogenetic abnormalities. Although it can affect any organ system, symptoms usually arise from involvement of the cerebral, pulmonary and renal microvasculature. The term "leukostasis" refers to 'symptomatic hyperleukocytosis' which is a medical emergency that needs prompt recognition and initiation of therapy to prevent renal and respiratory failure or intracranial haemorrhage. The underlying mechanisms of hyperleukocytosis and leukostasis are poorly understood. The management of hyperleukocytosis and leukostasis involves supportive measures and reducing the number of circulating leukemic blast cells by induction chemotherapy, hydroxyurea, low-dose chemotherapy, and leukapheresis. The measures such as hydroxyurea, low-dose chemotherapy, and leukapheresis shouldn't be considered to correct the laboratory abnormalities in patients with hyperleukocytosis who have no signs or symptoms. Also, neither hydroxyurea nore leukapheresis is able to show benefit on short and long term outcomes in patients with symptomatic hyperleukocytosis. The optimal management of symptomatic hyperleukocytosis is still uncertain, and there are no randomized studies demonstrating one is superior to each other. Therefore, it is recommended that intensive chemotherapy should be implemented as quickly as possible in treatment-eligible patients, in parallel with supportive measures for DIC and TLS.

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1. Introduction

Hyperleukocytosis has no definitive diagnostic criteria, however, it is classically defined as a white blood cell (WBC) count greater than 100.000/μL. Namely, hyperleukocytosis is a laboratory abnormality. Hyperleukocytosis is more common in patients with hematological malignancies, such as acute myeloid leukemia (AML), the microgranular variant of acute promyelocytic leukemia (APL), and acute lymphoblastic leukemia (ALL) [1]. The term 'leukostasis' is a medical emergency and called 'symptomatic hyperleukocytosis'. Leukostasis is a specific complication of hyperleukocytosis, and may result in laboratory abnormalities, such as tumor lysis syndrome (TLS), and disseminated intravascular coagulopathy (DIC). Also, outcomes are generally unfavorable and it has higher a mortality rate if left untreated. Leukostasis presents

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with respiratory, neurological, or renal compromise. However, there is not a good correlation between the threshold of WBC and/or blast count and the development of signs and symptoms of leukostasis, because some patients could have leukostasis with blast counts considerably lower than 100.000/μL [2,3]. In this paper, an overview of the epidemiology, pathophysiology, clinical presentation, and in particular current management options of hyperleukocytosis will be discussed.

2. Epidemiology

The incidence of hyperleukocytosis ranges from 5 to 13% in AML, and 10 to 30% in ALL. Hyperleukocytosis is often associated with AML FAB subtypes M4 and M5 [4], and also it has a high frequency in FLT3-ITD and MLL rearrangement positive AML [5]. Hyperleukocytosis is common in patients with ALL showing t(4;11) and t(9;22) [6]. It is also agreed that symptomatic hyperleukocytosis is higher in AML than in ALL [7]. Symptomatic hyperleukocytosis is rare in ALL and typically occurs with much higher WBC counts than in patients with AML. Since WBCs in chronic myeloid leukemia (CML) are usually segmented neutrophils, metamyelocytes, and myelocytes, which are smaller and more deformable than less mature cells, symptomatic hyperleukocytosis is very rare in this patient population, and mostly seen in the accelerated phase or blast crisis [8]. In patients with chronic lymphocytic leukemia (CLL), leukostasis has been mostly reported in patients with WBC counts greater than 1.000.000/μL [8].

3. Pathophysiology

The pathophysiology of leukostasis is not clear. There are two leading theories; (a) according to the rheological theory [9]; 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 respect to this proposed mechanism, myeloblasts are bigger than lymphoblasts and lymphocytes, therefore leukostasis is more frequent in AML than in ALL and CLL; (b) the other theory is based on the interaction of the blasts and the endothelium. Stucki et al. [10] demonstrated that endothelial cells activated by blasts secreted cytokines (TNF-α and IL-1β), and blast-endothelial cell interaction mediated by specific adhesion receptors (such as selectins and VCAM-1) play a major role in promoting blast cell adhesion to vascular endothelium. In addition, leukemic blasts have a higher rate of oxygen consumption and thus may compete with tissue cells in areas of obstructed flow [9]. Finally, blast cell aggregates can cause vascular occlusion, leading to ischemic tissue injury that can result in end organ damage such as intracranial hemorrhages and respiratory failure.

4. Clinical manifestations

The lungs and central nervous system are the most common organs affected in leukostasis. Respiratory symptoms include dyspnea, tachypnea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure, and diffuse interstitial or alveolar infiltrates in chest radiograph [11]. Neurological signs may include somnolence, confusion, dizziness, headache, tinnitus, confusion, blurred vision, delirium, stupor and coma [12]. Rare manifestations include acute leg ischemia, renal vein thrombosis, myocardial ischemia, bowel infarctions, fever, and priapism. Moreover, objective examination may reveal focal neurologic deficits, and retinal or intracranial hemorrhage [13]. Therefore, neurological, and fundoscopic examinations should not be neglected. A CT scan or MRI of the head may reveal intracranial hemorrhage. A chest X-ray or a CT scan often may show bilateral interstitial or alveolar infiltrates.

5. Diagnosis

The diagnosis of leukostasis is usually made by characteristic clinical signs in a patient with newly diagnosed acute and/or chronic leukemia. However, the clinical diagnosis is rarely made with high confidence. Whereas pathologically, the definition is clear and leukostasis can be defined as 'the morphological evidence of intravascular accumulation of leukemic blasts occupying most or all of the vascular lumen, with or without the presence of fibrin'[14]. In AML, leukostasis is seen most frequently in patients with WBC counts of 100.000/μL or greater. However, leukostasis was most prevalent in patients with ALL, whose WBC counts are above 400.000/μL. The laboratory abnormalities of hyperleukocytosis include marked leukocytosis, hypokalemia, pseudo-hyperkalemia, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia. Of note, a leukemoid reaction should be kept in mind in the differential diagnosis, so clinical history, examination of peripheral blood smear, and a total leukocyte count of less than 100.000/μL will likely distinguish hyperleukocytosis from the leukemoid reaction.

6. Management

Various interventions have been implemented in an attempt to improve outcomes in patients with symptomatic hyperleukocytosis. Most are supportive and include optimization of coagulation, hyperhydration, and allopurinol administration. Lichtman & Rowe showed that blood viscosity is not elevated in most hyperleukocytic states, because the increase of the leukocrit is usually compensated by a reduction of the erythrocrit [9]. For the same reason, blood product transfusions before leukapheresis should be avoided because it may trigger the development of leukostasis [15]. If needed, the transfusion should be administered slowly after the leukapheresis procedure. Additionally, diuretics may also lead to increased blood viscosity and should be delayed until the WBC count is decreased.

It is important to keep in mind that patients with hyperleukocytosis and leukostasis are also at increased risk of DIC and TLS [8]. DIC is a coagulopathy induced by the formation of small clots that consume coagulation proteins and platelets, resulting in a severe bleeding tendency. Acute DIC is characterized by a decrease in platelet count and fibrinogen, an elevation of D-dimers, and prolongation of prothrombin time and activated partial thromboplastin time and occurs in 30%–40% of AML patients with hyperleukocytosis [7]. Platelet transfusions and standard measures to restore normal coagulation such as substitution of fresh frozen plasma or fibrinogen should be initiated immediately in these patients. Platelet transfusion does not increase the risk of leukostasis significantly, conversely, red blood cell transfusion has a higher impact on blood viscosity than platelets. For stable patients with hemoglobin values higher than 7–8 g/dl, a red blood cell transfusion should be avoided.

In patients with leukostasis, TLS occurs in up to 10% of cases [16]. TLS may occur as a result of spontaneous or chemotherapy-induced cell death. Prevention strategies include hydration and prophylactic allopurinol [17]. Established TLS is managed similarly, with the addition of aggressive hydration (2–3 l/m^2/day) with the goal of hemodilution and reduction of viscosity and diuresis, plus allopurinol or rasburicase for hyperuricemia [17]. Additionally, electrolyte imbalances should be corrected properly.

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