Review

Leukostasis in adult acute hyperleukocytic leukemia: a clinician's digest

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Abstract

Leukostasis is a poorly understood and life-threatening complication of acute hyperleukocytic leukemia. The incidence of hyperleukocytosis and leukostasis differs among various subtypes of leukemias. While the pathophysiology of leukostasis is not fully understood, recent research has elucidated many novel pathways that may have therapeutic implications in the future. Respiratory and neurological compromise represents the classical clinical manifestations of leukostasis. If it is not diagnosed and treated rapidly, the one-week mortality rate is approximately 40%. Targeted induction chemotherapy is an important component of the successful treatment of leukostasis, although other modalities of cytoreduction are being used and investigated. Copyright © 2016 John Wiley & Sons, Ltd.

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Introduction

Hyperleukocytosis is classically and arbitrarily defined as white blood cell (WBC) count greater than 100 000 μL. Acute hyperleukocytic leukemias (AHL) represent the acute leukemias with initial total leukemia blood cell or blast count higher than 100 000 μL. However, the critical WBC count after which patients develop symptoms varies to a great extent based on the type of leukemia. While it is still debatable whether AHL represent a distinct subgroup of leukemias biologically and cytogenetically, it is well known that hyperleukocytosis is more common in patients with certain morphologic subtypes, such as AML with monocytic features. It is also known that AHL share a distinct clinical presentation with higher incidence rate of specific complications (leukostasis, tumor lysis syndrome, and disseminated intravascular coagulopathy) as well as generally unfavorable outcome and higher mortality rate.

Leukostasis, in contrast, should be viewed as a clinico-pathological entity. McKee and Collins defined leukostasis 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' [1]. Clinically, leukostasis is diagnosed in practice when a patient with leukemia and hyperleukocytosis presents with respiratory, neurological, or renal compromise. However, some patients could have clinically suspected or pathologically proven leukostasis with blast counts considerably lower than 100 000 μL [2,3]. Furthermore, many of the clinical, laboratory, and radiographic manifestations of leukostasis are indistinguishable from other complications of leukemia. There is a shortcoming of specific and reliable criteria for defining and diagnosing this condition, which represents along with the catastrophic consequences and high mortality if left untreated major challenges in this syndrome.

In this paper we provide an overview of the epidemiology, pathophysiology, clinical presentation, and treatment options for two aspects of leukemic malignancies: hyperleukocytosis and leukostasis.

Epidemiology

The incidence of hyperleukocytosis and leukostasis depends on the type of leukemia and the cytogenetic and phenotypic features of the leukemia. In several leukemias, an association was found between specific subtypes of the disease and leukocytosis. Herein, we present the most recent and important data on the epidemiology of hyperleukocytosis and leukostasis in the following leukemias: AML, ALL, CML, and CLL, which may aid in clarifying the pathophysiology of these entities in the future.

AML

While the incidence of hyperleukocytosis in AML varies from 5% to 20% in adult AML, leukostasis occurs less frequently [4–9]. Among the French–American–British (FAB) subtypes of AML, myeloid leukemias with monocytic

differentiation (M4, M5) [10] and the microgranular subtype (M3v) of acute promyelocytic leukemia (APL) [11] have been associated, in several studies, with hyperleukocytosis.

This association between monocytic leukemias and hyperleukocytosis was initially reported by Cuttner et al. [10], whose findings were later confirmed by other groups. For example, acute myelomonocytic leukemia with increased marrow eosinophils (M4Eo) usually presents with hyperleukocytosis and hepatosplenomegaly, and is uniquely associated with inversion of chromosome 16 [12]. Interestingly, despite the common presentation with hyperleukocytosis, the complete remission rate and overall survival in M4Eo are better than other subtypes of AML, which suggests that cytogenetics rather than hyperleukocytosis alone defines the prognosis [13]. In addition, hyperleukocytosis, organomegaly, and extramedullary involvement is a common presentation of monoblastic leukemia (M5a). However, unfavorable cytogenetics (rearrangements of 11q23) [14] and intermediate response to therapy are seen in M5a.

Other studies have attempted to investigate the association between hyperleukocytosis and specific karyotypes, hypothesizing that genetic mutations may play a role in unleashing the increased white blood cell count. In a cohort of 160 patients with AML, De Santis et al. detected a higher frequency of molecular mutations (NPM1, FLT3-ITD, and MLL-PTD) in the group of hyperleukocytic leukemias. Nevertheless, no statistical difference was observed when examining each mutation individually [15]. Still, some other studies reported an association between internal tandem duplications (ITD) of the FLT3 gene and hyperleukocytosis [16,17].

Finally, no association between hyperleukocytosis and age groups was reported in adult AML.

ALL

While the incidence of hyperleukocytosis in ALL is frequent and ranges between 10% and 30%, symptomatic leukostasis is rare and typically occurs with much higher WBC counts than in patients with AML.

A clearer and more concrete association between hyperleukocytosis and distinct immunophenotypic and cytogenetic subtypes of ALL can be identified. Cytogenetically, t(4;11) and t(9;22) (Philadelphia chromosome-positive ALL) have been associated with hyperleukocytosis and poor prognosis [18–20]. Another translocation that has been linked to hyperleukocytosis and implies a poorer prognosis is t (1;19) [21,22].

Phenotypically, a strong association between the expression of T-cell markers and hyperleukocytosis in ALL has been reported [23,24]. Other reported associations include the presence of mediastinal mass and the leukemic involvement of CNS at diagnosis, male sex, and massive hepatosplenomegaly [24].

CML

Although patients with chronic myeloid leukemia often present with hyperleukocytosis with WBC counts greater than 100,000 μL, symptomatic leukostasis is very rare and occurs almost exclusively in the accelerated phase of the disease or patients with blast crisis [25,26]. One potential explanation for this finding is that white blood cells in CML are usually segmented neutrophils, metamyelocytes, and myelocytes, which are smaller and more deformable than less mature cells (blasts).

CLL

While hyperleukocytosis, with total WBC counts in excess of 100,000 μL is often seen in CLL [27], symptoms and signs related to leukostasis are rarely seen. Leukostasis has been reported mostly in patients with WBC counts greater than 1 000 000 μL [28–31].

Pathophysiology

The biological and pathophysiological background of leukostasis is not clear. It has been hypothesized that organ hypoxia is the main pathophysiological change in leukostasis. However, the mechanisms behind the tissue hypoxia are not well understood (Figure 1).

Lichtman et al. suggested that leukostasis occurs when the viscosity of the blood increases and flow of blood in the microcirculation is impeded [32,33]. They demonstrated in vitro studies that a dramatic rise in viscosity occurs when the fractional volume of leukocytes (leukocrit) exceeds 12–15 ml/dL. However, leukocrit is a function of not only WBC counts, but also the mean cell volume (MCV) of the cells, and the MCV of leukemic myeloblasts is twice as large the MCV of leukemic lymphoblasts. This partially accounts for the higher incidence of leukostasis in AML compared to ALL. In addition, the viscosity is related to the deformability of the individual cells. This also may explain the higher incidence of leukostasis in acute leukemias compared to chronic leukemias because leukemic blasts are considerably less deformable than mature leukocytes.

Although this proposal may provide a logical interpretation for the underlying pathophysiology of leukostasis, much remains unclear. For example, Lichtman [34] and others showed that blood viscosity is not elevated in most of hyperleukocytic leukemias because the increase of the leukocrit is usually compensated by a reduction of the erythrocrit. The significant management application of this phenomenon is that RBC transfusion in patients with AHL may trigger the development of leukostasis and should be avoided [35]. Moreover, the leukemic blast numbers necessary to reach a leukocrit of 12–15 mL/dL
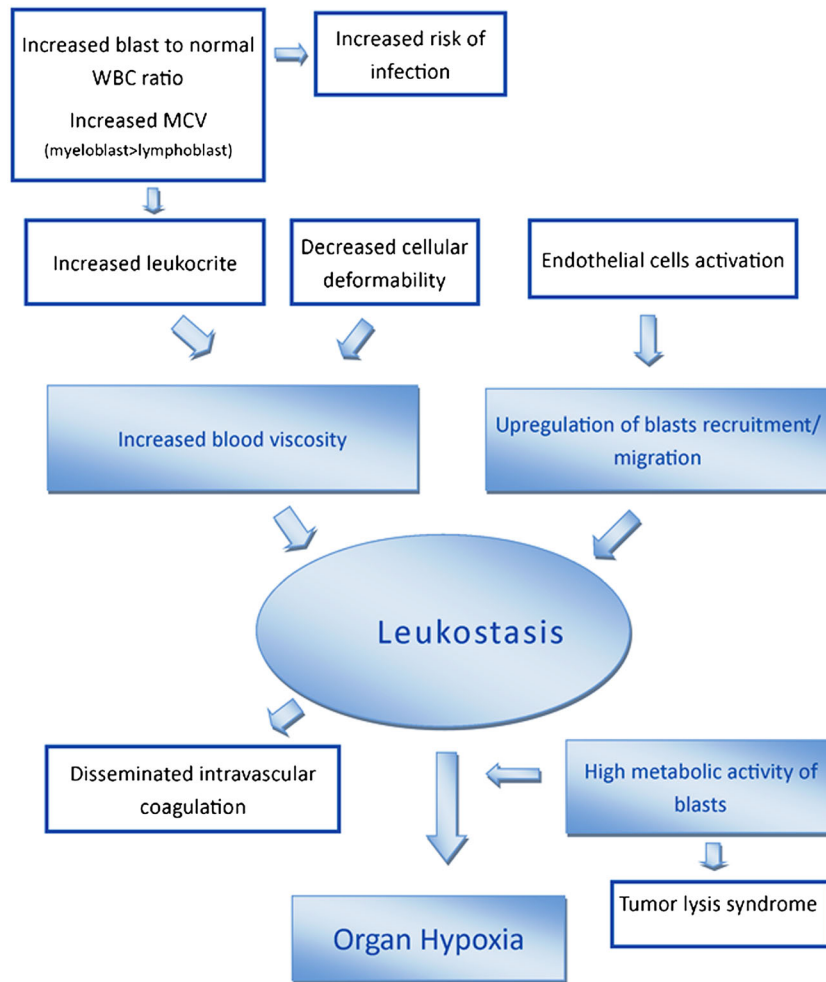
Figure 1. Pathophysiology of leukostasis

are rarely seen (300 000–450 000 in AML and 600 000–800 000 in ALL). Moreover, patients may develop clinically suspected or pathologically proven leukostasis even with significantly lower blasts counts [2,3]. Hence, although blood viscosity may play a role in leukostasis, other factors are implicated. Finally, autopsy studies of patients with leukostasis have shown that blast aggregates are encountered more frequently in lung, brain and heart, suggesting that leukostasis is not simply related to blast counts or the biomechanical features of the cells but also a result of blast migration with a degree of organ specificity [1].

The lack of a clear and full explanation of the pathophysiology of leukostasis with hyperviscosity theory has led to increasing interest in studying an alternative or supplemental explanation. Based on observation such as the established role of specific adhesion molecules in neutrophil-induced acute lung injury in sepsis [36,37] and the expression and function of adhesion receptors in leukemic cells [38–43], it has been hypothesized that adhesions receptors and cytokines secreted by blast cells play a key role in leukostasis.

In Stucki et al. studies, endothelial cells were shown to be activated by cytokines secreted by blasts (TNF, IL-1b), followed by upregulation of several adhesion molecules (i.e. selectins and VCAM-1), leading to blast cells recruitment and adhesion to vascular endothelium in AML patients with leukostasis [44]. This leukemic blast–endothelial cell interaction may lead to vascular wall disruption, perivascular tissue infiltration, and hemorrhage that add to the hypoxic damage already present from reduced blood flow [44–46]. Another supporting observation is the changes in type and number of adhesion receptors induced by all-trans retinoic acid (ATRA) therapy, leading to leukostasis in the context of retinoic acid syndrome that some patients with APL develop upon therapy with ATRA [47]. It is also possible that complement may play a role in granulocyte aggregation and hyperleukocytic syndrome [48,49]. These findings may open the door for novel therapies for leukostasis and leukemic tissue infiltration. The identification of more adhesion molecules, cytokines, and receptors mediating these pathological processes may allow for the development of cytokine inhibitors and adhesion receptor antagonists that may ultimately have important therapeutic implications.

Finally, it is also possible that local hypoxemia caused by the mechanisms mentioned above may be exacerbated by the high metabolic activity of the dividing blasts, another possible explanation for the high incidence of symptomatic leukostasis in acute myeloid leukemia (with high mitotic activity) compared to chronic lymphocytic leukemias.

Hyperleukocytosis and risk stratification in leukemia

Hyperleukocytosis has significant prognostic implications in both AML and ALL, especially when accompanied by clinical evidence of leukostasis, such as neurologic symptoms and respiratory distress. Some authors suggested that AML patients who present with hyperleukocytosis have lower complete remission (CR), disease free survival (DFS), overall survival (OS), as well as high rate of early mortality [4]. Others showed that only high early mortality (or induction death ID) was affected by leukocytosis [50]. Among these patients with early mortality, lethal hemorrhagic events and infection were the most common causes of death. Many other studies confirmed the significant impact of presenting leukocyte count in determining induction mortality in adult AML [51,52]. However, it is still controversial whether hyperleukocytosis represents an independent prognostic factor from other established markers, such as cytogenetics, gene mutations, and overexpression of multidrug resistant phenotype. Establishing this prognostic significance of hyperleukocytosis in AML is critical, as these patients with hyperleukocytosis represent a considerable proportion of all AML cases that may be candidates for allogeneic bone marrow transplantation; therefore, accurate risk stratification in this population is crucial. In all types of ALL, more consistent data regarding the impact of hyperleukocytosis on prognosis can be found in the literature [53–55].

It is still unclear whether the prognostic impact of hyperleukocytosis in different types of leukemias underscores a fundamental biological difference or is simply a consequence of high tumor burden.

Clinical presentation and diagnosis

Clinical signs of leukostasis are protean and non-specific. From a clinicians' perspective, leukostasis should be perceived as a prothrombotic disorder with increased blasts playing the major role in the clotting process. This occurs because of the morphological and functional characteristics of the increased blasts [56]. It is important to note that there is no widely accepted minimum leukocyte count for the diagnosis of hyperleukocytosis and leukostasis.

A patient with leukostasis may present with shortness of breath, cough, and hypoxemia requiring ventilator support [57,58]. Radiological studies play an important role in the diagnostic work up of respiratory complaints in patients with leukostasis. Chest X-ray (CXR) may be normal or show the alveolar pattern of infiltrates [58]. Furthermore, pulmonary leukostasis can radiologically mimic tuberculosis and pulmonary embolism in the appropriate clinical setting [59,60]. In the vast majority of cases, respiratory symptoms of leukostasis present before the leukemia targeted treatment is initiated, although rare patients may worsen after initiation of induction chemotherapy [61]. This decline is believed to occur secondary to therapy-related changes in leukocyte membrane and the release of procoagulant chemicals from dying leukocytes [61]. Pulmonary symptoms carry the worst prognostic burden in patients with leukostasis with poor short-term survival rates [62,63].

.Central nervous system (CNS) manifestations of leukostasis may include confusion, altered mental status, focal neurological deficits, and possibly seizures [26,64–66]. Fundoscopic exam, often neglected by physicians, may establish the diagnosis when papilledema, dilated blood vessels, and retinal hemorrhages are present. Brain imaging, either computed tomography (CT), or magnetic resonance imaging (MRI) may reveal ischemic areas, areas of hemorrhages, or CNS masses. Of note, very rare cases of pathologically confirmed that CNS leukostasis may lack laboratory evidence of hyperleukocytosis [65].

Other potential clinical presentation of leukostasis may include deep venous thrombosis [31], avascular bone necrosis [67], acute appendicitis [68], sudden cardiac death because of right-sided cardiac mass [69], splenic rupture [70], acute kidney injury [71,72], retinopathy [73], and fever.

Laboratory abnormalities other than marked leukocytosis may include true hypokalemia [72], pseudo hyperkalemia because of cellular death in vitro (collect heparinized plasma), hyperkalemia, and other laboratory abnormalities due tumor lysis syndrome (hypocalcemia, hyperuricemia, and hyperphosphatemia) [74]. Special attention should be focused on the estimation of platelet counts manually, because automatic cellular counters may overestimate platelet count (some white blood cells will be counted as platelets). Accurate assessment of the platelet count is important for several reasons: first, most hematological malignancies are associated with thrombocytopenia; second, leukostasis targeted treatment may lower the platelet counts (e.g. leukapheresis, chemotherapy); finally, patients with leukostasis are predisposed to bleeding and hemorrhages in addition to vascular occlusion. Hypoxemia may be true or lower than its actual value (pseudohypxemia) because of the oxygen uptake by malignant cells (leukocyte larceny syndrome). One potential solution for these patients may include the use of pulse oximetry, although that may be less than ideal in cases of profound hypoxemia and shock, at least until white blood count is decreased.

There is no defined WBC count that would correspond to the clinical syndrome of leukostasis. Novotny et al. studied 95 patients with various forms of leukemia such as AML, ALL, CML, and chronic myelomonocytic leukemia (CMML) with a baseline WBC >50 000 to devise a leukostasis grading score for use in clinical practice [75]. Researchers divided these patients into four different groups (no leukostasis syndrome, possible, probable, and highly probable leukostasis syndrome) based on the severity of pulmonary, neurological, and other symptoms. Picirrillo et al. validated the leukostasis grading score in their separate study [76]. The leukostasis grading score is shown in Table 1. However, the vast majority of patients with leukostasis also present with hyperleukocytosis; very few patients may have normal WBC and pathologically confirmed leukostasis [65]. Despite the development of grading system to predict leukostasis, it remains a clinical diagnosis in a symptomatic patient with hyperleukocytosis after excluding other etiologies.

Management

Leukostasis is a true medical emergency, and all patients should be admitted and managed in the intensive care unit (ICU) unless against patient's wishes (Figure 2). It is important to keep in mind that patients with hyperleukocytosis and leukostasis are also at increased risk of disseminated intravascular coagulation [77] and tumor lysis syndrome (TLS) [74]. Clinicians caring for these patients should monitor for these complications, instituting prompting corrective measures and treatments. Furthermore, patients with symptomatic leukostasis should be worked up for possible concomitant etiologies of their symptoms such as pneumonia, meningitis, and encephalitis among many others. The work-up should be tailored to the clinical presentation and may include chest imaging, brain imaging, blood cultures, and cerebrospinal fluid analysis provided no contraindications. Patients with leukostasis should be started on empiric antibiotics after collection of microbiological data. Empiric antibiotics may be stopped at a later date provided there are no microbiologically positive cultures and a low clinical suspicion for an infectious culprit. Treatments that may lead to increased blood viscosity such as diuretics and blood products transfusions should be delayed until the white count is decreased, unless deemed essential. If needed, the transfusion should be administered slowly during or immediately after leukapheresis.

All women of child-bearing age should be screened for pregnancy, and consultation with obstetrics is strongly advised in cases of confirmed pregnancy. It is also important to emphasize that hematology consultation is essential in all cases of suspected leukostasis. Unfortunately, the presence of leukostasis is associated with high short and long-term mortality rates compared to patients without leukostasis [6,78].

Management options for leukostasis include induction chemotherapy for the culprit hematological malignancy, non-specific cytoreductive therapy with hydroxyurea, leukapheresis, radiation therapy, and corticosteroids. There have been no prospective randomized trials or large observational studies comparing these options, and it is unlikely that trials will be feasible given the emergent nature of this condition, urgency of decision making, and strong physician preferences. Below we will briefly discuss each of these modalities (Figure 2).

Induction chemotherapy

Whether or not a patient presenting with leukostasis has a previously diagnosed hematological malignancy, it is imperative to perform an analysis of peripheral smear and bone marrow before initiating induction chemotherapy.

Table 1. Leukostasis grading score (adapted from reference #22)

| Group	Probability of leukostasis	Severity of symptoms	Pulmonary symptoms	Neurologic symptoms	Other organ systems
0	Not present	No limitations	No symptoms and no limitations in ordinary activities	No neurologic symptoms	No symptoms
1	Possible	Slight limitations	Mild symptoms and slight limitations during ordinary activity, but comfortable at rest	Mild tinnitus, headache, dizziness	Moderate fatigue
2	Probable	Marked limitations	Marked limitations in activity because of symptoms, even during less than ordinary activity, comfortable only at rest	Slight visual disturbances (such as diplopia, blurry vision, and hemianopia), severe tinnitus, headache, dizziness	Severe fatigue
3	Highly probable	Severe limitations	Dyspnea at rest, need for respiratory support including mechanical ventilation	Severe visual disturbances, confusion, delirium, coma, cerebral catastrophes, seizures	Myocardial infarction, priapism, other ischemic events
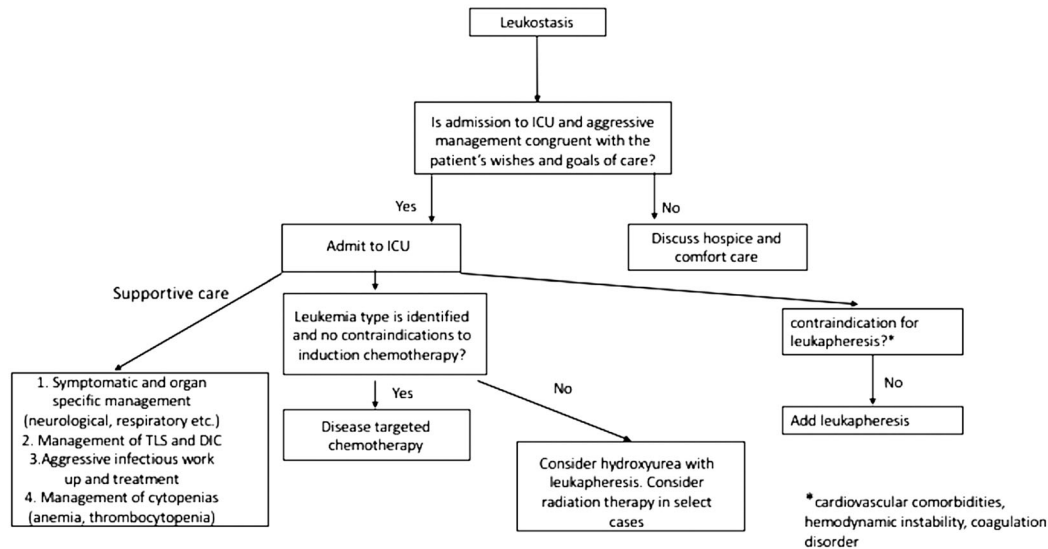
Figure 2. Management of leukostasis

Low-dose chemotherapy (along with hydroxyurea and leukapheresis) has been used in AML patients with hyperleukocytosis in attempt to achieve gradual cytoreduction in order to lower the tumor burden and reduce the risk of TLS. However, a recent systematic review showed that this approach did not have an impact on the early mortality in these patients [79]. The meta-analysis failed to show any superiority of this approach to standard-dose chemotherapy. Furthermore, TLS has become less problematic in the era of urate oxidase. In light of these findings, the thresholds of using low-dose chemotherapy and hydroxyurea should be reconsidered. An alternative strategy would be to initiate targeted induction chemotherapy, along with urate oxidase and supportive measures, as soon as the leukemia type is identified, with no preceding cytoreduction. Chemotherapy provides a rapid decrease in WBC count and also targets the blast cells in the bone marrow, thus, providing a more sustained response [80]. However, this strategy should be evaluated rigorously before fully implemented in practice.

Some patients may deteriorate after the initiation of chemotherapy [61]. Of particular importance is the fact that patients with suspected APL should be started on ATRA because of high mortality rates and good response to treatment [81,82]. Of note, 50% of patients who are treated with ATRA alone at induction experience hyperleukocytosis, likely because of rapid maturation of a large mass of leukemic cells. Therefore, it is imperative to combine ATRA with cytotoxic chemotherapy for APL patients with high WBC at presentation. Anthracycline-based chemotherapy combined with ATRA remains the recommended initial therapy in APL cases with hyperleukocytosis. Nevertheless, many groups have investigated combining ATRA with other agents. Arsenic trioxide (ATO) has been added to ATRA in many studies, and often caused WBC count to rise raising concerns regarding differentiation syndrome. Although gemtuzumab ozogamicin [83] or hydroxyurea have been used in these situation to reduce the rising WBC, this approach remains controversial with less robust evidence.

Leukapheresis

Leukapheresis remains an important modality for the management of leukostasis awaiting the diagnostic work-up. Leukapheresis should be used in patients with symptoms of leukostasis provided there is no contraindication (cardiovascular comorbidities, hemodynamic instability, or coagulation disorders). Leukapheresis usually requires insertion of a central venous catheter unless bilateral cubital or cephalic veins are appropriate for peripheral large bore cannulation [84]. The potential complications of the procedure include venous access related adverse events (bleeding, infection, thrombosis, pneumothorax), hypocalcemia (citrate is used as the anticoagulant for the procedure and may bind calcium), and loss of other blood products (platelets, red blood cells). A single session of leukapheresis may decrease the WBC count by approximately 25–50% [84]. However, leukapheresis does not remove blasts from the bone marrow, and the WBC count may quickly rebound once the session is complete. Furthermore, patients with rapidly proliferating leukemias may not respond to leukapheresis at all [85].

The data regarding the impact of leukapheresis on patients' outcome and survival is scant and controversial. While some early published cases reported a reduction in symptom burden [86–89], some studies even demonstrated a beneficial impact on the short-term mortality [90,91], whereas others did not [79,92]. Current data suggest that

leukapheresis has no impact on long-term mortality [90]. Leukapheresis should not be used in patients with the acute promyelocytic variant of AML because of possible worsening of coagulopathy and DIC [11].

Hydroxyurea

Hydroxyurea may be used as a cytoreductive agent and bridging strategy in patients with not yet diagnosed hematological malignancy or with contraindications to induction chemotherapy [93–95]. Hydroxyurea acts via inhibition of ribonucleoside diphosphate reductase leading to impairment of deoxyribonucleic acid (DNA) synthesis and DNA repair. The typical dose of hydroxyurea is 50–100 mg/kg a day in two divided doses [94]. Hydroxyurea works more slowly than induction chemotherapy, and the cytoreductive effect should be expected to occur within 24–48 h [94]. Hydroxyurea also decreases the blood viscosity in patients with leukemia likely through its cytoreductive effect [96].

Cranial radiation

Brain and retinal irradiation have been used in the management of the patient with CNS symptoms attributed to leukostasis [97]. From the theoretical perspective, this treatment may be beneficial in terms of reducing the number of blast cells within the CNS where the concentration of chemotherapy drugs may be suboptimal. However, there is a paucity of scientific data on the role of brain irradiation and its impact on the outcomes; therefore, it is not considered a first-line approach to management.

Steroids

In the observational study performed by Azoulay et al. dexamethasone, in addition to standard chemotherapy, improved outcomes in patients with acute monocytic leukemia (AML type M5) and hypoxic respiratory failure requiring mechanical ventilation [98]. It has been proposed that that dexamethasone inhibits up-regulation of adhesion molecules in leukemic and endothelial cells (selectins, VCAM-1, IL-8 receptors, CD-18). Further studies are needed to validate the beneficial effects of steroids and their potential use in other types of leukemias with associated leukostasis and organ damage.

Novel therapies

Novel approaches are needed to reduce the early mortality rate in patients with leukostasis. It is hoped that a better understanding of the pathological pathways of this condition, including the surface adhesions molecules and chemotactic cytokines, will lead to the development of inhibitors that target the interaction between leukemic cells and vascular endothelium. Such novel pharmacological strategies may lead to a more effective therapy and a reduction in the early mortality associated with leukostasis.

Conclusion

Leukostasis in the setting of AHL is a hematologic emergency. More efforts are required to establish specific and reliable criteria for defining and risk stratifying these conditions. Research should focus on understanding the pathophysiology of leukostasis and tissue infiltration by leukemic cells, and therefore opening the doors for novel therapeutic interventions.

Conflict of interest

The authors declare that there are no conflicts of interest.

Financial disclosure

The authors have nothing to disclose.

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