Blood Reviews 29 (2015) 291–299

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Transfusions for anemia in adult and pediatric patients with malignancies

Neil Shah [a], Jennifer Andrews [a,c], Lawrence Tim Goodnough [a,b,*]

[a] Department of Pathology, Stanford University, USA
[b] Department of Medicine, Stanford University, USA
[c] Department of Pediatrics, Stanford University, USA

ARTICLE INFO

Keywords:
Anemia
Red blood cell transfusion
Restrictive vs liberal transfusion practices

ABSTRACT

Anemia is present in over two-thirds of patients with malignant hematological disorders. The etiology of anemia predominates from ineffective erythropoiesis from marrow infiltration, cytokine related suppression, erythropoietin suppression, and vitamin deficiency; ineffective erythropoiesis is further exacerbated by accelerated clearance due to antibody mediated hemolysis and thrombotic microangiopathy. As the anemia is chronic in nature, symptoms are generally well tolerated and often non-specific. Transfusion of red blood cells (RBCs) is a balance between providing benefit for patients while avoiding risks of transfusion. Conservative/restrictive RBC transfusion practices have shown equivalent patient outcomes compared to liberal transfusion practices, and meta-analysis has shown improved in-hospital mortality, reduced cardiac events, re-bleeding, and bacterial infections. The implications for a lower threshold for transfusion in patients with malignancies are therefore increasingly being scrutinized. Alternative management strategies for anemia with IV iron and erythropoietin stimulating agents (ESAs) should be considered in the appropriate settings.

1. Introduction

Blood transfusion therapy is a key component of supportive care for adults and children with malignant hematologic disorders such as leukemia and recipients of hematopoietic stem cell transplants (HSCT). Over two-thirds of patients with a hematologic malignancy develop anemia [1], with the highest prevalence in children with leukemia (over 97%) and lymphoma (over 93%) [2]. The transfusion of red blood cells (RBC) is a balance between the benefits of maintaining oxygen delivery and the inherent risks from blood transfusion. We have previously published reviews of blood transfusion practices in adults [3] and in the elderly [4]; and here, we update blood transfusion therapy in adults and children. We summarize the pathophysiology of anemia in this setting, indications for red blood cell (RBC) transfusion, current blood risks, special situations in RBC transfusion, and alternative or adjunct therapy for anemia management such as erythropoietic stimulating agents (ESAs) and iron therapy. Where possible, we provide evidence-based guidelines for best practices.

2. Pathophysiology of anemia in patients with malignant hematologic disorders

The anemia in this setting is multifactorial and includes production defects, accelerated clearance, and hemorrhage. Causes of anemia include leukemic infiltration of the bone marrow at diagnosis or relapse, chemotherapy and radiation therapies, suppression of the erythropoietin response to anemia, infection/inflammation, shortened RBC survival, or hemorrhage secondary to thrombocytopenia and/or consumptive coagulopathies such as disseminated intravascular coagulation [5].

Anemia in patients with leukemia is most often due to underproduction of erythropoietic precursors, because of direct tumor infiltration of the bone marrow or chemotherapies [6]. In patients undergoing HSCT, radiotherapy and preparative myeloablative chemotherapy regimens further challenge RBC precursor production. Ninety six percent of adult patients receiving myeloablative chemotherapy preparations require RBC support, compared to only 63% of patients receiving non-myeloablative preparations [7].

Reduced and ineffective erythropoiesis in the form of renal dysfunction (reduced erythropoietin) and cytokine mediated anemia of chronic disease (ACD) also contribute to anemia in patients with hematologic malignancies. Tumor-released cytokines upregulate hepcidin [8,9] which leads to sequestration of body iron stores in bone marrow macrophages and reduced iron absorption from the alimentary tract. Hepcidin degrades ferroportin receptors, which are responsible for making iron available for erythropoiesis, through iron transport from enterocytes and marrow macrophages into plasma [10].

Red cell precursors may also selectively be reduced: i.e. pure red cell aplasia, due to ABO-incompatible HST [11], underlying lymphoproliferative disorder [12], certain drugs [13], and formation of antibodies to erythropoietin [14]. Less frequent contributing causes of erythropoiesis suppression include viral suppression of erythropoiesis as occurs with

* Corresponding author at: Department of Pathology, Stanford University, 300 Pasteur Dr., Room H-1402, Stanford, CA 94305-5626, USA. Tel.: +1 650 723 6037.

http://dx.doi.org/10.1016/j.blre.2015.02.001
0268-960X/

various infections including parvovirus B19. Renal insufficiency and vitamin deficiencies such as iron, folate or vitamin B12 may also contribute to anemia in adult patients, as illustrated in Fig. 1 [4].

Shortened RBC survival can also accompany the anemia of underproduction in malignancy. Lymphoproliferative conditions such as chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma, and lymphoplasmacytic lymphoma are associated with warm and cold reactive autoantibodies to RBCs [15]. Fludarabine and other purine analogs also increase the frequency of autoimmune hemolytic anemias (AHA) [16]. Laboratory findings in AHA typically include a low hemoglobin, high lactate dehydrogenase (LDH), high bilirubin (typically indirect), low haptoglobin, hemoglobinuria and positive direct antiglobulin test (DAT) for IgG classically in a warm AHA and complement (or C3d) in a cold AHA.

Malignancies and targeted therapies have also been associated with microangiopathic hemolytic anemia (MAHA) and disseminated intravascular coagulation (DIC). While acute DIC is uncommon presentation for most hematologic malignancies, urokinase-like plasminogen activator has been found in blasts of acute promyelocytic leukemia (APL) which often lead to DIC prior to widespread treatment with all-trans retinoic acid [17,18]. Chemotherapy agents such as cisplatin, bleomycin, daunorubicin, and calcineurin inhibitors used in HSCT patients such as cyclosporine and tacrolimus have been shown to independently lead to drug-induced MAHA [19].

3. Clinical manifestations of anemia

The signs and symptoms of anemia vary based on the acuity of the anemia, the compensatory change in blood volume and the compensatory change in the patient's cardiovascular system. Chronic anemia is generally well tolerated due to compensatory expansion of intravascular plasma volume, increased cardiac output, vasodilatation, increased blood flow due to decreased viscosity, and not least, increased RBC 2,3 diphosphoglycerate (DPG) with a right shift of the oxygen dissociation curve. Symptoms of anemia are often non-specific and can include fatigue, pallor, dizziness, headaches, vertigo, tinnitus, dyspnea,

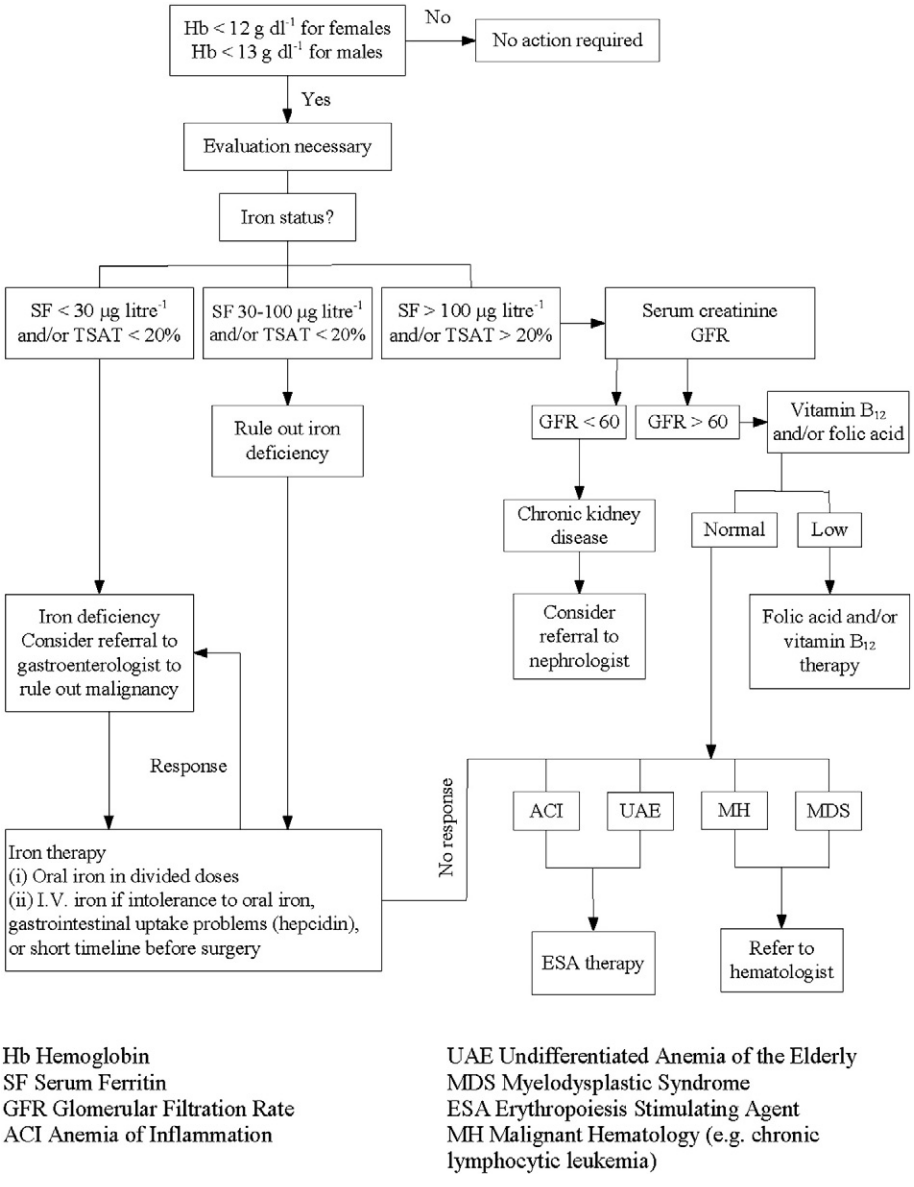

Fig. 1. Evaluation and management of anemia. Once the blood count demonstrates anemia, an evaluation should begin with an assessment of iron status. When ferritin and/or iron saturation levels indicate absolute iron deficiency, iron therapy is indicated. When ferritin and/or iron saturation values rule out absolute iron deficiency, serum creatinine and glomerular filtration rate (GFR) determination may indicate chronic kidney disease (CKD). When ferritin and/or iron saturation values are in determinant, further evaluation to rule out absolute iron deficiency versus inflammation/chronic disease is necessary. A clinical response to a therapeutic trial of iron would confirm absolute iron deficiency. No response to iron therapy would indicate the anemia of chronic disease, suggesting that ESA therapy be considered. Reproduced with permission From Goodnough LT, Schrier A. Am J Hematol 2014;89:88–96 [4].