

Workup of Anemia in Cancer

Sidharth Anand, MD, MBA,¹ Aaron Burkenroad, MD, MS,² and John Glaspy, MD, MPH^{1,a}

¹Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, California

²Division of Internal Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California

^aSenior author

Corresponding author:

Sidharth Anand, MD, MBA

UCLA Health

2020 Santa Monica Blvd, Ste 600

Santa Monica, CA 90404

E-mail: sanand@mednet.ucla.edu

Tel: (818) 448-2900

Abstract: Anemia is a common diagnosis in patients with cancer that may affect both quality of life and survival. Anemia in this patient population is often multifactorial, caused by direct effects of the malignancy, products secondary to the malignancy, the effects of treatment, or other factors. Therefore, a systematic approach is required to determine the true cause or causes of anemia. An appropriate workup of anemia in patients with cancer can lead to treatment with the potential to reduce transfusion needs and improve quality of life. The clinical benefit of these interventions for specific patients must be weighed against possible risk.

Background

Anemia is one of the most common complications of cancer and cancer treatment. It is estimated that 20% to 60% of patients with cancer have anemia at their initial diagnosis, termed anemia of cancer (some of these patients may have anemia that is unrelated to their malignancy, which is beyond the scope of this paper). The percentage of patients with cancer who have anemia increases to 60% to 90% during cancer therapy; this subset of patients with anemia of cancer is said to have chemotherapy-induced anemia.^{1,2} The 2 established sequelae of anemia in patients with cancer are symptoms of anemia and an increased likelihood of the need for red blood cell (RBC) transfusions.

Anemia is usually multifactorial in patients with cancer; possible contributing factors include bleeding, nutritional deficiencies, hemolysis, reduced erythropoietin levels, inflammation with increased hepcidin activity, and the toxic effects of chemotherapy in marrow precursors. It is important to identify the causes of anemia to select an appropriate treatment strategy. The goals of treatment are to reduce the likelihood of a transfusion requirement and to enhance functional status.

A less well-established sequela of anemia in patients with cancer is a potential negative effect on cancer survival or the efficacy of treatment.^{3,4} Although many studies have documented an association between significant anemia and reduced cancer survival, the link may simply reflect a worsening of anemia in patients with more advanced cancers.^{3,5}

Pathophysiology of Anemia of Cancer

An understanding of the pathophysiology of anemia of cancer is important because it can guide the workup and treatment of

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patients with this condition. Anemia of cancer is typically mediated by cytokines produced in malignancy, such as interferon (IFN), tumor necrosis factor (TNF), and interleukin (IL), all of which can suppress erythropoiesis (Figure). Suppression may result from the inhibition of iron metabolism and utilization via an increase in the iron regulatory protein hepcidin, which in turn leads to the sequestration of iron in macrophages. In addition, cytokines decrease the production of erythropoietin by inhibiting messenger RNA synthesis.⁶

The diagnosis of anemia of inflammation is often one of exclusion. Patients who have this condition typically have normal iron stores with a normal transferrin saturation. Systemic inflammation in cancer leads to the production of inflammatory cytokines, such as IL-1 β , IL-6, IL-10, and IFN- γ , all of which have broad effects on RBC production, RBC life span, and iron metabolism.⁷ In inflammation, RBC damage occurs via free radical-mediated injury as well as inadvertent immune complex and fibrin deposition, which increase RBC phagocytosis and destruction by macrophages.^{7,8} During this process, iron retention by macrophages is increased via increased ferritin production and the blockage of iron export as a result of the inhibition of iron exporter ferroportin (FP1) production.⁹

Erythropoiesis and erythroid differentiation are also impaired in inflammatory states. Specifically, erythropoietin (EPO) production by kidney epithelial cells is inhibited by cytokines such as IL-1 β , TNF- α , and IFN- γ .¹⁰ Expression of the EPO receptor is downregulated in this setting. In addition, TNF- α has been shown to inhibit EPO-mediated erythroid differentiation, and IFN- γ has been shown to induce erythroid progenitor apoptosis via the Fas pathway.^{10,11}

Systemic inflammation leads to activation of the hepcidin pathway, which has broad effects on iron metabolism. Specifically, cytokines such as IL-1 β , IL-6, and lipopolysaccharide (LPS) induce the production and activation of hepcidin in the liver.¹² Hepcidin increases iron retention in macrophages and decreases dietary iron absorption in the duodenum, in both cases via the degradation of FP1.⁹ These effects cause hypoferrinemia and hyperferritinemia, making iron less available for erythropoiesis.

Under hypoxic conditions, hypoxia inducible factor 1 (HIF-1) is thought to induce the synthesis of EPO and vascular endothelial growth factor, as well as other growth factors. Heme is synthesized by protoporphyrin IX, a by-product of glucose metabolism. Iron is involved in the regulation of EPO synthesis in conjunction with the hypoxia-inducible factor 2 α (*HIF2A*) gene. Iron regulatory genes bind the renal *HIF2A* gene's iron-responsive elements, thereby modulating the translation of HIF. An

iron-dependent enzyme, prolyl hydroxylase, catalyzes the degradation of HIF-2 α , which is negatively related to hypoxia.¹³ In cancer-related anemia, tumor- and macrophage-derived proinflammatory cytokines such as IL-6 increase the production of hepcidin in the liver, resulting in a decrease in HIF and subsequently EPO. This functional iron deficiency pathway leads to a further decrease in erythropoiesis.

Therefore, cancer-related inflammation is theorized to cause anemia through shortened RBC survival resulting from increased destruction, suppressed erythropoiesis due to a decrease in erythropoietin, suppressed bone marrow erythropoiesis, and iron-restricted erythropoiesis due to an increase in hepcidin.¹⁴

Differential Diagnosis

Often, the easiest way to differentiate cancer-related anemia (which mimics the anemia of chronic inflammation) from anemia with other causes is by considering the patient's initial presentation. Those patients who present with anemia before receiving any cancer-directed therapy often have cancer-related anemia, and they most often have advanced malignancy. Cancer-related anemia, similar to the anemias of chronic inflammation, tends to be hypoproliferative, with a low reticulocyte index, and to have normochromic, normocytic indices. Iron studies demonstrate reduced serum iron and reduced total iron-binding capacity. The ferritin level can be either low or elevated as a consequence of malignancy.¹⁵ One interesting way to distinguish iron deficiency anemia from anemia of chronic disease is by measuring the ratio of soluble transferrin receptor to ferritin. A low ratio is likely consistent with anemia of cancer; the EPO level also tends to be low in the setting of anemia of cancer.¹⁶ Ferritin can occasionally be elevated by acute inflammation or the underlying malignancy. RBCs are typically normochromic and normocytic on the peripheral blood smear, but they can also appear hypochromic and microcytic.

Direct Effects of Malignancy

Anemia can result from direct effects of cancers owing to their occupation of space in the body, resulting in endothelial damage, impaired absorption, and marrow replacement. It is useful to have an understanding of these potential etiologies when determining a course of treatment.

A tumor may cause bleeding by damaging endothelium—for example, by damaging the lining of the GI or genitourinary tract—or it may bleed into itself. The tumor that most commonly bleeds into itself is hepatocellular carcinoma, which can potentially lead to liver rupture. Other malignancies implicated in internal

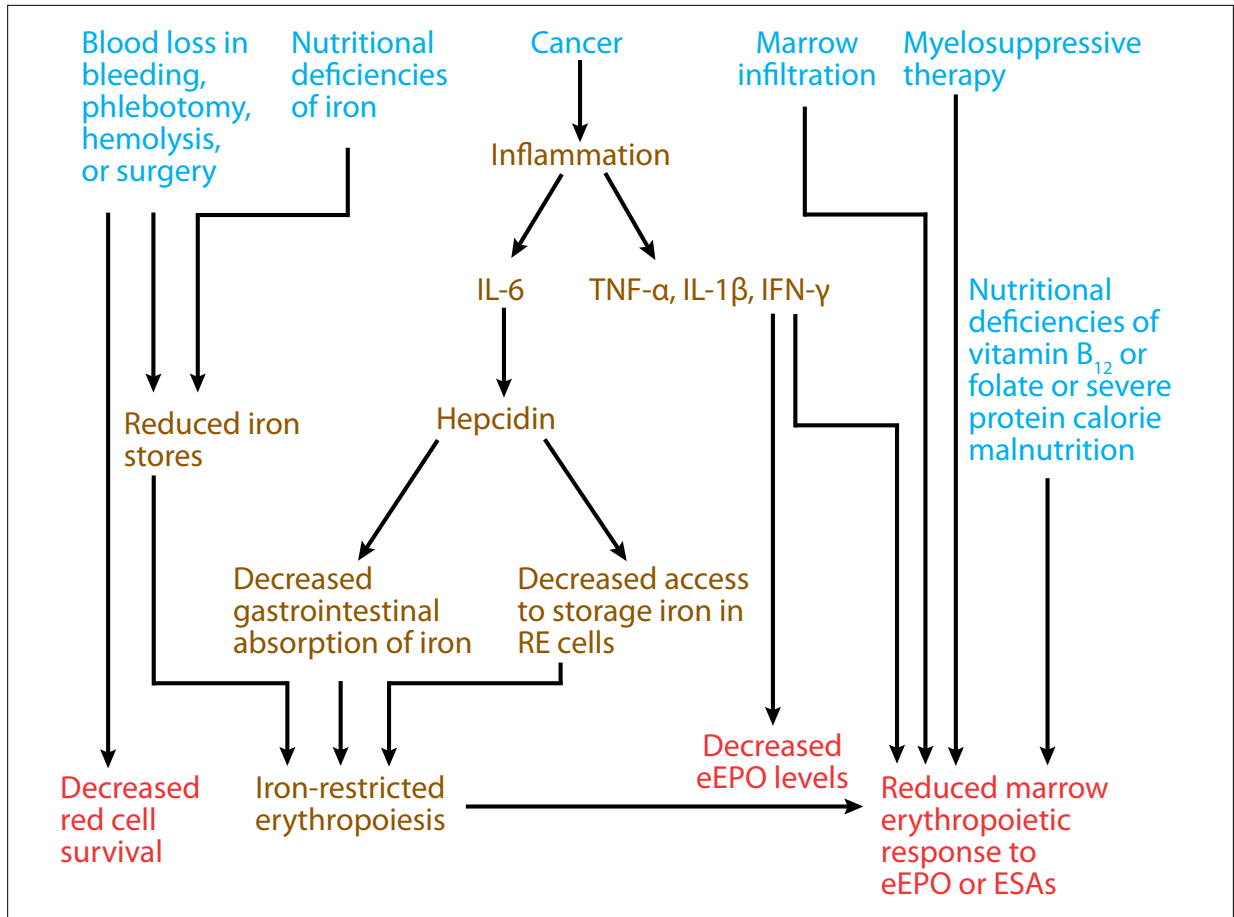


Figure. The pathogenesis of anemia in patients with cancer. Multiple mechanisms can cause anemia in these patients. Underlying inflammation leads to cytokine production (TNF- α , IL-1 β , IFN- γ , and IL-6), which causes anemia via a decrease in endogenous erythropoietin production and negative effects on iron metabolism via the hepcidin pathway. Blood loss and nutritional deficiency can both lead to a reduction of iron stores, which causes iron-restricted erythropoiesis. This effect, as well as myelosuppressive therapies, bone marrow infiltration, and other nutritional deficiencies (vitamin B₁₂, folate, and protein), can result in a poor response to endogenous erythropoietin or ESAs.

eEPO, endogenous erythropoietin; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; IFN, interferon; IL, interleukin; RE, reticuloendothelial; TNF, tumor necrosis factor.

hemorrhage include splenic hemangiosarcomas, liver metastases from ocular or cutaneous melanomas, and cavernous hemangiomas.

The workup of anemia in this setting often reveals iron deficiency anemia, characterized by the presence of microcytic, hypochromic RBCs on the peripheral smear. Iron deficiency anemia leads to a decrease in the mean corpuscular volume and mean corpuscular hemoglobin, and eventually a decrease in the serum ferritin level and transferrin saturation. Stool and urine samples are key to identifying a potential source of bleeding.

Endothelial damage can also cause anemia through the initiation of disseminated intravascular coagulation (DIC), which can take place through the release of tissue

factor, an activator of factor VII that is expressed on tumor cells. This process ultimately results in a degradation of coagulation factors and an increase in fibrin degradation products.

Workup generally reveals a few peripheral blood schistocytes, an elevated prothrombin time (PT)/international normalized ratio/activated partial thromboplastin time (aPTT), a decrease in fibrinogen, and an increase in D-dimer and other fibrin degradation products.

Malignancies can also impede the absorption of vital nutrients needed for the creation of RBCs. For example, cancers of the duodenum or upper jejunum may interfere with iron absorption, and cancers that affect the stomach or terminal ileum may affect the absorption of intrinsic

factor and vitamin B₁₂. Absorption can be impeded in cases of amyloid deposition in multiple myeloma and gastrointestinal malignancies, and especially as a post-treatment effect of surgical interventions for these malignancies.

Finally, malignancies can lead to bone marrow replacement, especially hematologic malignancies such as multiple myeloma, leukemia, and lymphoma. Bone marrow metastases from a variety of solid tumors can also cause bone marrow replacement. Bone marrow replacement results in the inhibition of hematopoiesis, which can cause myelophthisis, anemia, and extramedullary hematopoiesis in the liver and spleen. Workup usually reveals teardrop RBCs and nucleated RBCs in the peripheral blood smear, and immature granulocytes.

Products Secondary to Malignancy

Tumors and tumor by-products can be antigenic, leading to immune-mediated anemias. For example, the presence of immunoglobulin G or complement component 3d on the surface of circulating red blood cells can cause autoimmune hemolytic anemia. This most often occurs in hematologic malignancies, such as chronic lymphocytic leukemia (CLL), multiple myeloma, and lymphoma. The diagnosis is usually established by the presence of markers of hemolysis, including increased indirect bilirubin, increased lactate dehydrogenase (LDH), and reduced haptoglobin. In addition, the peripheral smear usually demonstrates spherocytes. The direct antiglobulin (Coombs) test result is positive.

Solid and hematologic malignancies can directly cause microangiopathic hemolytic anemia (MAHA). In addition, infections that occur in the setting of malignancy can cause conditions such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and DIC. From a clinical perspective, solid malignancies tend to cause a more thrombotic presentation of DIC, whereas hematologic malignancies often lead to a more hemorrhagic presentation. The diagnosis of MAHA is generally based on evidence of thrombocytopenia as well as microangiopathic changes on the blood smear. Differentiating between DIC and TTP/HUS can be challenging, but platelet consumption generally occurs in TTP/HUS, whereas the PT and activated PTT are usually normal. Levels of fibrinogen and D-dimer help to distinguish between these as well, given that both are generally abnormal in DIC (decreased fibrinogen, increased D-dimer) and generally normal in TTP/HUS.

Acute promyelocytic leukemia (APL) is an example of a cancer that produces factors leading to anemia. The anemia results from DIC, and tissue factor, cancer procoagulant, and annexin II are involved in the process. Cancer procoagulant is a calcium-dependent cysteine protease that activates factor X; tissue factor also activates factor

X through the formation of a complex with factor VII. Annexin II, expressed on leukemia cells in APL, binds plasminogen and tissue plasminogen factor, leading to an increase in plasmin formation. This causes coagulopathy and severe DIC. Management involves treating the underlying cause. In this case, all-trans retinoic acid (ATRA) is used to block transcription of the annexin II gene. ATRA should be used on an emergency basis to increase tumor cell differentiation and decrease coagulopathy.

CLL and tumors such as thymomas may lead to pure red cell aplasia, which is characterized by a hypoproliferative anemia, with a significant decrease in erythroid progenitors in the bone marrow. Management often involves resection of the thymoma or the treatment of CLL, in addition to immunosuppression in some cases.

Treatment-Related Anemia

Cancer treatment, including surgery, radiation, chemotherapy, targeted agents, and immunotherapy, may have profound effects on marrow function and cause anemia.

Surgery is often used to treat cancer. Some surgeries can result in the malabsorption of nutrients that are essential for RBC creation, particularly iron and vitamin B₁₂. For example, partial or total gastrectomy can lead to achlorhydria, or possibly intrinsic factor deficiency. Surgeries that involve resection of the terminal ileum may also cause vitamin B₁₂ malabsorption, although this likely takes many years to manifest as a deficiency owing to existing stores of vitamin B₁₂ in the liver.

Radiation can cause lasting bone marrow damage and affect the creation of RBCs, particularly if the radiation field encompasses a significant portion of the bone marrow.

Chemotherapy can have a lasting effect on the bone marrow, with temporary or permanent marrow suppression. In some cases, the administration of treatment leads to infections that cause marrow suppression (eg, parvovirus B19). Similarly, targeted agents may have off-target effects that impair RBC production, and immunotherapy can lead to autoimmune hemolytic anemia.

Finally, particular treatments have unique effects that may be implicated in new-onset anemia in patients with cancer. For example, some formulations of biosimilar erythropoietin have led to acquired pure red cell aplasia caused by anti-erythropoietin antibodies. With the advent of new biosimilars for a variety of other small molecules, concerns exist for the possible development of additional treatment-related anemias.

Workup Strategy

In conducting the workup of anemia in a patient with cancer, it is prudent for the clinician to consider the differential diagnoses discussed above. Clinicians should seek to categorize the anemia clinically and biologically

and determine a pretest probability of the likely cause of the anemia in question. The differential should be kept broad to include the many relevant possibilities that may be contributing to the patient's anemia. Clinically, it is helpful to determine the acuity of the presentation and understand how symptomatic the patient is. This approach will guide the urgency of the clinician's interventions. Some features of particular clinical presentations may be helpful, such as physical signs of nutritional deficiencies and/or hemolysis. Biologically, it is helpful to understand the characteristics of the malignancy that is involved, especially if it has features that may provide clues regarding the etiology of the anemia in question. Anemia of cancer must be differentiated from anemia with other causes because this can have implications for treatment. For example, colon cancer may lead to acute blood loss anemia, whereas acute promyelocytic leukemia and microangiopathy (DIC)-related anemia

It is important to keeping the differential diagnosis broad but examine all possible categories—direct effects of the malignancy, products secondary to the malignancy, effects of treatment, and other factors—because the causes of malignancy-associated anemias are often complex. For example, the clinician may attribute a microcytic anemia in gastric cancer to chronic blood loss, but a sudden drop in hemoglobin may point to thrombotic microangiopathy caused by gemcitabine.

The laboratory evaluation of these cancer-related anemias is generally standard, involving the tools discussed in the previous section. However, clinical suspicion based on pretest probability should guide the weight that the clinician places on any of these factors.

The initial workup of anemia in patients with cancer should include an examination of the peripheral blood smear, a reticulocyte count, and a determination of the iron indices and levels of ferritin, LDH, and haptoglobin. Additional testing can be undertaken on the basis of the pretest probability calculation for various other potential etiologies, described previously. For example, if thrombotic microangiopathy (TMA) is suspected, D-dimer, PT, and activated PTT testing may be helpful. In certain cases of malignancy-related malabsorption, levels of intrinsic factor antibody and serum vitamin B₁₂ should be evaluated. Evaluating the serum levels of erythropoietin and soluble transferrin receptor may also be used in cases of suspected anemia of cancer. Finally, a direct Coombs test may be done and the folate level may be checked in settings in which the index of suspicion for a hemolytic anemia is high.

Treatment

The treatment of anemia in patients with cancer requires a careful understanding of the potential etiologies previously

described. Although management of cancer-related anemia has historically relied on use of packed RBC transfusion, particular agents have been used in an attempt to reduce transfusion dependence. These additional treatments can be administered intelligently and safely with a clear understanding of their features.

In general, the treatment of anemia in the patient with cancer is directed at the underlying malignancy. In the case of bleeding anemias, for example, which often occur in gastrointestinal cancer, management involves control of the bleeding, often on an urgent basis. Surgical resection is often employed, as are interventional radiology techniques such as angiography and embolization. Another treatment option is the transfusion of packed RBCs.

For patients with an iron deficiency-related or a vitamin B₁₂ deficiency-related anemia, treatment is aimed at simple replacement. Treatment options become more complicated in patients with hemolytic anemia, DIC, or anemia related to TMA, but management often relies on treatment of the underlying malignancy, in addition to the use of tools such as apheresis when clinically indicated.

The basis of the ideal management of anemia due to chronic inflammation, or cancer-related anemia, is treatment of the underlying condition, iron supplementation via iron therapy or transfusions, and the use of erythropoiesis-stimulating agents (ESAs) in selected patients. However, iron replacement, transfusion, and ESA use can in turn lead to their own complications, and the efficacy of treatment is limited by the effects of hepcidin overexpression.¹⁷

Clinical Benefits of ESA Use in Patients With Cancer

Currently, ESAs—including epoetin alfa (Epogen, Amgen; Procrit, Janssen Biotech) and darbepoetin alfa (Aranesp, Amgen)—have received regulatory approval for use in patients with chemotherapy-induced anemia, an important subset of patients with anemia of cancer.^{18,19} An important benefit of ESA therapy in these patients is a decrease in the need for blood transfusions, by approximately 50%.^{20,21} Interestingly, in studies evaluating ESA use in patients with cancer and anemia that is not attributed to chemotherapy, a reduction in transfusion requirements has not been observed. Owing to safety concerns regarding the use of ESAs in this setting, high-quality studies with sufficient power have not been performed.²² However, improvements in patient-reported outcomes related to symptom burden, including a reduction in fatigue and an increase in productivity, have been reported.^{23,24} To date, the majority of studies conducted on ESA use in patients with cancer have not demonstrated improvement in treatment response or survival. A 2010 meta-analysis of 60 controlled studies showed a small, nonsignificant effect of ESA use on mortality in

the setting of chemotherapy-induced anemia. In the same analysis, no significant effect on disease progression was observed.²⁵

Safety Concerns With ESA Use in Patients With Cancer

Multiple meta-analyses of controlled studies have demonstrated that ESA therapy is associated with an increased risk for venous thromboembolism (VTE).^{26,27} Although the specific mechanism of this increased risk is unknown, multiple pathways have been proposed. ESA administration expands the RBC mass, which in turn causes an increase in viscosity and vasoconstriction, both of which are thought to portend a higher risk for thrombosis.²⁸ ESAs can cause an absolute or relative iron deficiency via iron-dependent erythropoiesis, which has been shown to lead to thrombocytosis.²⁹ Because thrombocytosis is a risk factor for cancer-associated VTE, this effect may serve as another mechanism of ESA-associated thrombotic risk.³⁰ This hypothesis was tested via a retrospective analysis of a trial in which patients with chemotherapy-induced anemia were randomly assigned to receive weekly epoetin alfa and intravenous ferric gluconate, oral ferrous sulfate, or no iron for 8 weeks. Interestingly, VTE was 3 times as likely to occur in the patients whose platelet counts increased to values of at least 350,000/ μL during the study.³¹ Rates of VTE were independent of the use of parenteral iron. However, given that the concurrent administration of parenteral iron has been shown to reduce the platelet count and improve rates of response to ESAs, its use may be considered a means of improving both the efficacy and safety of these agents.

Targeting the Hepcidin Pathway

Targeting of the hepcidin pathway represents the next therapeutic frontier in the management of cancer-related anemia.

Multiple targets can be exploited to inhibit hepcidin activity, either by directly inhibiting hepcidin itself or by binding ferroportin and preventing its interaction with hepcidin while leaving iron export unaffected.³² Multiple small-molecule inhibitors and monoclonal antibodies have been developed and are under investigation in clinical trials. For example, Pieris Pharmaceuticals is developing PRS-080, a PEGylated (coupled with polyethylene glycol) anticalin (an engineered polypeptide) that neutralizes hepcidin. The safety of this agent was verified in a phase 1 trial, and results from a phase 2 trial are forthcoming. Another agent, NOX-H94 (or lexaptedip pegol), is a PEGylated Spiegelmer (a synthetic ribonucleotide polymer) that inactivates hepcidin via direct binding. This agent, which is being developed by NOXXON Pharma, was shown in a phase 2 trial to achieve elevations in serum hemoglobin and decreases in ferritin in patients with

hematologic malignancies.^{33,34} These data suggest that pharmacologic targeting of the hepcidin pathway can be effective in ameliorating anemia in patients with anemia of chronic inflammation, but more work is needed to identify which agents will be most successful.

Conclusion

Anemia is extremely common in cancer patients and has meaningful effects on symptomatic burden and quality of life. Diagnostic workup requires a thoughtful and comprehensive laboratory evaluation based on each patient's presentation and symptoms. Proper understanding of the individual patient's etiology is essential to guide treatment. Adequate management relies on treatment of the underlying malignancy and correction of existing iron and/or other nutritional deficiencies. Packed RBC transfusion is also often a cornerstone of management, but can lead to worsened quality of life. For patients with chemotherapy-related anemias, ESAs are approved but have important safety concerns that include increased risk of VTEs and possibly deleterious effects on tumor progression and/or patient survival. More work is needed to understand how to mitigate safety concerns with ESAs in these patients. Recent early-phase clinical trials of investigative therapies aimed at inhibition of the hepcidin pathway have been completed that demonstrate adequate safety. Advanced-phase trials of these therapies are needed to determine their efficacy in reducing transfusion requirements and symptom burden. Importantly, these agents eventually may be used in a broader subset of patients in whom ESAs cannot be used owing to approval issues or previously described safety concerns. We hope that they will one day be used in combination with—or in place of—the therapeutic tools that are currently available.

Disclosures

Drs Anand, Burkenroad, and Glaspy have no conflicts of interest to disclose.

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