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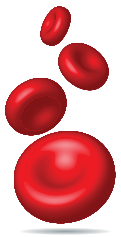
Diagnosis and treatment of cancer-related anemia



Jeffrey A. Gilreath,[1] David D. Stenehjem,[1,2] and George M. Rodgers[3,4]*

Cancer-related anemia (CRA) is due to multiple etiologies, including chemotherapy-induced myelosuppression, blood loss, functional iron deficiency, erythropoietin deficiency due to renal disease, marrow involvement with tumor as well as other factors. The most common treatment options for CRA include iron therapy, erythropoietic-stimulating agents (ESAs), and red cell transfusion. Safety concerns as well as restrictions and reimbursement issues surrounding ESA therapy for CRA have resulted in suboptimal treatment. Similarly, many clinicians are not familiar or comfortable using intravenous iron products to treat functional iron deficiency associated with CRA. This article summarizes our approach to treating CRA and discusses commonly encountered clinical scenarios for which current clinical guidelines do not apply.
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Introduction

Treatment of cancer-related anemia is a controversial subject. Prior to 2006, it was assumed that erythropoietic stimulating agents (ESAs) were safe and effective when used to treat anemic cancer patients who were or were not receiving chemotherapy. However, in 2006, clinical trial data were reported demonstrating a safety signal for ESAs in these populations [1]. Subsequently, the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) promulgated warnings and restrictions on the use of ESAs in cancer patients [2]. Publication of later clinical trials specifically designed to address mortality of ESA therapy in anemic cancer patients receiving chemotherapy suggested no safety signal [3,4]. However, there has been a dramatic reduction in the use of ESAs in these patients [2,5], despite treatment guideline recommendations [6,7]. This article summarizes our approach to managing adult anemic cancer patients, which may include the correction of nutritional deficiencies, use of intravenous (IV) iron, ESAs, and blood transfusions.

What is Cancer-Related Anemia?

The pathogenesis of cancer-related anemia (CRA) is multifactorial and can be a direct result of cancer invasion (anemia secondary to cancer [ASC]), its treatment (radiation), or chemotherapy-induced anemia [CIA]), or chronic kidney disease (CKD) (Fig. 1). ASC is a direct result of the malignancy invading normal tissues causing blood loss, marrow infiltration which inhibits production of red cells, or inflammation leading to functional iron deficiency. Myelosuppressive chemotherapy either alone or in combination with radiotherapy commonly contributes to the development of anemia and is referred to as CIA [7]. CKD, a result of renal injury from tumor invasion, chemotherapy, or age-related decline can be diagnosed in the majority of elderly patients with cancer [8]. Although patients may have several of the aforementioned contributing factors for anemia, the etiology of CRA can always be traced back to the production, destruction, or loss of red blood cells (RBCs).

Production

The predominant mechanisms for ASC, CIA, and CKD are reduced erythropoiesis from several factors. These include reduced erythropoietin (Epo) production secondary to acute kidney injury or CKD [9,10], nutritional deficiencies of iron, folate, and vitamin B_{12}, or bone marrow injury due to bone metastases, myelodysplasia, or myelosuppressive chemotherapy [11,12]. Pure red cell aplasia can occur in patients with thymoma, leukemia, or lymphomas due to tumor-associated cytokines, or rarely from induction of anti-Epo antibodies after exogenous Epo use [13–15]. Additionally, patients with malignancies arising from hematopoietic progenitors or precursors (i.e., the acute and chronic leukemias) frequently present with anemia. This may result, in part, due to hyperproliferation of bone marrow blast cells which "crowd out" the non-malignant cell population thus preventing normal erythroid blast-forming units and islands from interacting with stem cell factor and bone marrow stromal cells which are thought to be necessary to maintain their differentiation, growth, and division [16,17]. Additionally, mutations in or therapy-related inhibition of the intracellular domain of c-kit (CD117) may also be partly responsible for reduced erythropoiesis by reducing c-kit-dependent phosphorylation and the intracellular interaction between c-kit and the tyrosine kinase domain of the erythropoietin receptor [18–20].

[1]Department of Pharmacy, Huntsman Cancer Institute, University of Utah Hospitals and Clinics, Salt Lake City, Utah; [2]Department of Pharmacotherapy, Pharmacotherapy Outcomes Research Center, College of Pharmacy, University of Utah, Salt Lake City, Utah; [3]Department of Medicine, University of Utah Hospitals and Clinics, Salt Lake City, Utah; [4]Department of Pathology, University of Utah Hospitals and Clinics, Salt Lake City, Utah

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***Correspondence to:** George M. Rodgers, Division of Hematology and Hematologic Malignancies, University of Utah Hospitals and Clinics, 30 North 1910 East, Salt Lake City, UT 84132. E-mail: george.rodgers@hsc.utah.edu
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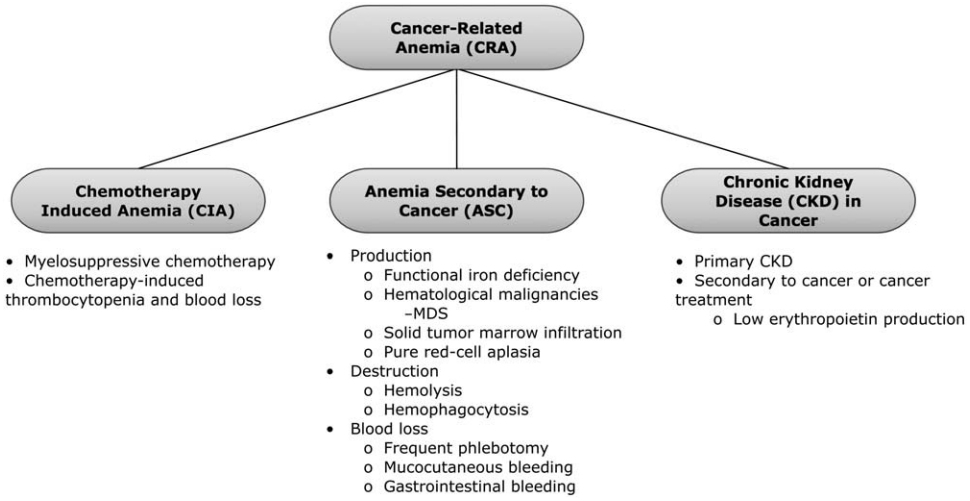

Figure 1. Types of Cancer-Related Anemia.

Destruction

Destruction of RBCs can result from consumptive processes such as autoimmune hemolytic anemia seen in chronic lymphocytic leukemia, or erythrophagocytosis in histiocytic tumors [21–23], or microangiopathic processes [24]. Hypersplenism with sequestration of hematopoietic cells is also common in myeloproliferative neoplasms, lymphoid malignancies, or in cancers invading the spleen or inducing portal hypertension.

Loss

Loss of RBCs resulting in anemia can occur from treatment-related factors (blood loss during surgery or from frequent phlebotomy for laboratory testing) [25], and tumor-related bleeding observed with gastrointestinal or uterine cancers.

What is the Prevalence of Cancer-Related Anemia?

Prevalence data vary depending upon many factors, including type of cancer, definition of anemia (<9 g/dL vs. <11 g/dL), disease stage, and whether patients have been treated. A literature review in 2004 described prevalence rates between 30 and 90% [26]. Additionally, a 2004 European Cancer Anaemia Survey (ECAS) reported that at survey entrance, 39% of cancer patients were anemic prior to treatment [27].

Our Approach to Cancer-Related Anemia

At our institution, we have a collaborative practice agreement, which allows pharmacists specializing in hematology/oncology to manage and prescribe agents (under protocol) used in the treatment of CRA [28]. Our approach to treating CRA begins with concurrently assessing severity and identifying correctable causes of anemia (Fig. 1). In our initial workup, we assess and direct therapy towards cancer-associated anemia factors related to the production, destruction, or loss of red cells. We also assess renal function prior to myelosuppressive chemotherapy and screen for the subsequent development of renal insufficiency, as ESAs may be used (albeit judiciously) under CKD protocols. Patients can have overlapping types of CRA, and treatment pathways can be conflicting; therefore clinicians will need to determine the course of treatment likely to offer the greatest benefit while minimizing the risks of therapy. Our preferred treatments are listed in Table I.

Nutritional Deficiencies (Folate, Vitamin B_{12}, and Iron)

In 1998, the FDA began an initiative to eliminate folate deficiency through fortification of whole grains, rice, and cereal products sold in the United States. Afterwards, the prevalence of folate deficiency decreased to less than one percent of the population [38]. We reviewed serum folate and vitamin B_{12} concentrations in anemic cancer patients at our institution. Folate and B_{12} deficiency were detected in 0% (0/127 vs. <0.6% in general population) and 3.9% (5/129 vs. 3.9% in general population, $P = 1.0$) of patients, respectively (Table II, unpublished data). Our internal data corroborate the results of a study by Henry et al. [39] in which 226 cancer patients were screened for folate and vitamin B_{12} deficiency. None of the patients were folate deficient. In fact, 80% of patients had increased serum concentrations of folate. In addition, only 7% (16/226) of patients were deficient in vitamin B_{12}. Table II compares our results with those of Henry et al. [39], and nation-wide cohort studies [38,40]. Because of the low prevalence of vitamin deficiency in the general population and in patients with cancer, we reserve testing for serum folate or B_{12} concentrations in patients with high clinical suspicion such as overt laboratory signs or clinical symptoms such as an increased MCV or neurological symptoms. We also test for folate and vitamin B_{12} deficiency when ESA treatment is planned, as many insurance groups require excluding vitamin deficiency with laboratory tests prior to starting an ESA. Once baseline deficiency is excluded, we do not recommend further testing after commencing ESA therapy. Unlike iron deficiency, ESA hyporesponsiveness due to vitamin deficiency (folate or B_{12}) has only been cited in one case report [41] to our knowledge. If vitamin B_{12} deficiency is present at baseline, we prefer the use of oral vitamin B_{12} 2,000 mcg by mouth once daily for 3 months [29]. For patients with folate deficiency at baseline, we prescribe 1 mg by mouth daily for 3 months. We assess for correction of vitamin deficiency after 3 months (Fig. 2) [31].

A 2012 literature review reported a 29–60% prevalence of iron deficiency in cancer patients in five separate studies, all using a different definition of iron deficiency [42]. In anemic cancer patients, approximately 63% of patients had TSAT and ferritin concentrations

TABLE I. Recommended Medications for the Treatment of Cancer-Related Anemia

		Dose	Route	Frequency	Specifically studied in cancer patients?
B-Vitamins					
Cyanocobalamin[a] [29,31,101]		1,000 mcg	IM	Days 1–10, then monthly OR Days 1, 3, 7, 10, 14, 21, then monthly	No
		2,000 mcg[b,c]	PO	Daily × 90 days	No
Folic Acid [31]		1–5 mg	PO	Daily × 90 days	No
Erythropoietic stimulating agents					
	CKD	50–100 units/kg	SQ	Three times weekly	No
Epoetin alfa [30]	CIA	40,000 units	SQ	Once weekly	Yes
		80,000 units[b,c]		Every 2 weeks	Yes
		120,000 units[b]	SQ	Every 3 weeks	Yes
	CKD	0.45 mcg/kg[d]	SQ	Every 4 weeks	No
Darbepoetin alfa [32]	CIA	200 mcg[b,c]	SQ	Every 2 weeks	Yes
		300 mcg[b,c]	SQ	Every 3 weeks	Yes
		500 mcg	SQ	Every 3 weeks	Yes
IV iron formulations[e,f]					
Low-molecular weight Iron Dextran [33]		200–400 mg	IV	Over 1 hr × until 1 g administered	Yes
Iron sucrose [35]		200 mg[c]	IV	Over 5 min weekly × 5 doses total	Yes
Sodium ferric gluconate [34]		125 mg	IV	Over 60 min weekly × 8 doses total	Yes
Ferric carboxymaltose [36]		1,000 mg	IV	IV Push (1,000 mg over 10 min)	Yes

[a] Cyanocobalamin should not be given IV as there is little opportunity for liver storage resulting from rapid excretion into the urine after administration [102].
[b] Non-FDA approved; CKD: Chronic kidney disease; CIA: Chemotherapy-induced anemia.
[c] Author's treatment preferences.
[d] Although FDA-approved dose for non-dialysis dependent CKD patients is 0.45 mcg/kg SubQ every 4 weeks, a higher dose (0.75 mcg/kg SQ every 2 weeks, FDA-approved for dialysis-dependent CKD) is often needed for cancer patients with CKD (authors' experience). This "higher" dose is still less than doses typically used for CIA.
[e] Ferumoxytol has not been studied as treatment for iron deficiency in patients with cancer.
[f] Iron dose recommendations are based on the administration of 1 gram of iron.

TABLE II. Prevalence of Folate and Vitamin B_{12} Deficiencies in Patients with Cancer and the General Population

	Anemic Cancer Patients at the Hunts-man Cancer Institute (2006–2008)[a]	Henry and Dahl [39]	United States Population (NHANES [38])	United States Population >50 years [40]
Folate Deficiency	0% (0 of 127 patients)	0% (0 of 216 patients)	<0.6% (46 of 7,692 patients)	0.1% (2 of 1,546 patients)
Vitamin B_{12} Deficiency	3.9% (5 of 129 patients)	7% (16 of 226 patients)	3.9% (300 of 7,692 patients)	2.7% (41 of 1,546 patients)

[a] Unpublished data from Burt LE, et al.

below levels recommended to prevent iron-restricted erythropoiesis [39]. Therefore, because of the high prevalence of iron deficiency, it is our standard of practice to assess iron studies (transferrin saturation or TSAT, serum ferritin) in symptomatic cancer patients who are mildly anemic (Hb 10–12 g/dL) and in all patients who are severely anemic (Hb <10 g/dL).

Iron Replacement Therapy

Historically, the treatment of CRA has focused on using ESAs with or without iron; however, our treatment approach is to first consider iron with or without an ESA. In many practices, iron studies are often only assessed when a transfusion or an ESA is being considered to treat severe or symptomatic anemia. As a result of the latter scenario, these assays are often ignored, iron is not administered, and an alternative means of anemia treatment (e.g., blood transfusion) is pursued [43]. Before starting an ESA, iron studies are recommended to exclude a pre-existing iron deficiency, since stimulating erythropoiesis requires bioavailable iron for an optimal response [1,7,44,45]. Additionally, just as with vitamin deficiencies, many insurers require normal iron studies prior to reimbursing ESA therapy.

Candidates for iron therapy

The goal of iron therapy is to safely and effectively correct anemia in cancer patients with either absolute iron deficiency (AIDA: TSAT < 20%; ferritin < 30 ng/mL) or functional iron deficiency (FIDA: TSAT 20–50%; ferritin 30–800 ng/mL) (Fig. 2) [2,7]. These definitions are loosely derived using data from studies which prospectively enrolled cancer patients receiving an ESA in addition to IV iron [44–50]. Unfortunately, each of the studies used different inclusion criteria for baseline TSAT and ferritin values, which makes interpretation of the results difficult. Additionally, the definitions of AIDA and FIDA may differ for specific disease states (CKD vs. cancer-related anemia), as the response to iron therapy may depend on the underlying etiology of iron deficiency. For example, the KDIGO (Kidney Disease Improving Global Outcomes) guidelines define AIDA for CKD patients as ferritin <30 ng/mL (no TSAT requirement) and recommend a trial of iron therapy in patients with a TSAT ≤30% and ferritin ≤500 ng/mL [10]. We believe that the present definitions for AIDA and FIDA in cancer patients provide conservative guidance for the administration of IV iron, as the optimal dosing and frequency, as well as target TSAT and ferritin ranges for a variety of anemic patients with cancer have yet to be defined. Importantly, these IV iron studies have not examined mortality, infection, venous thromboembolism,

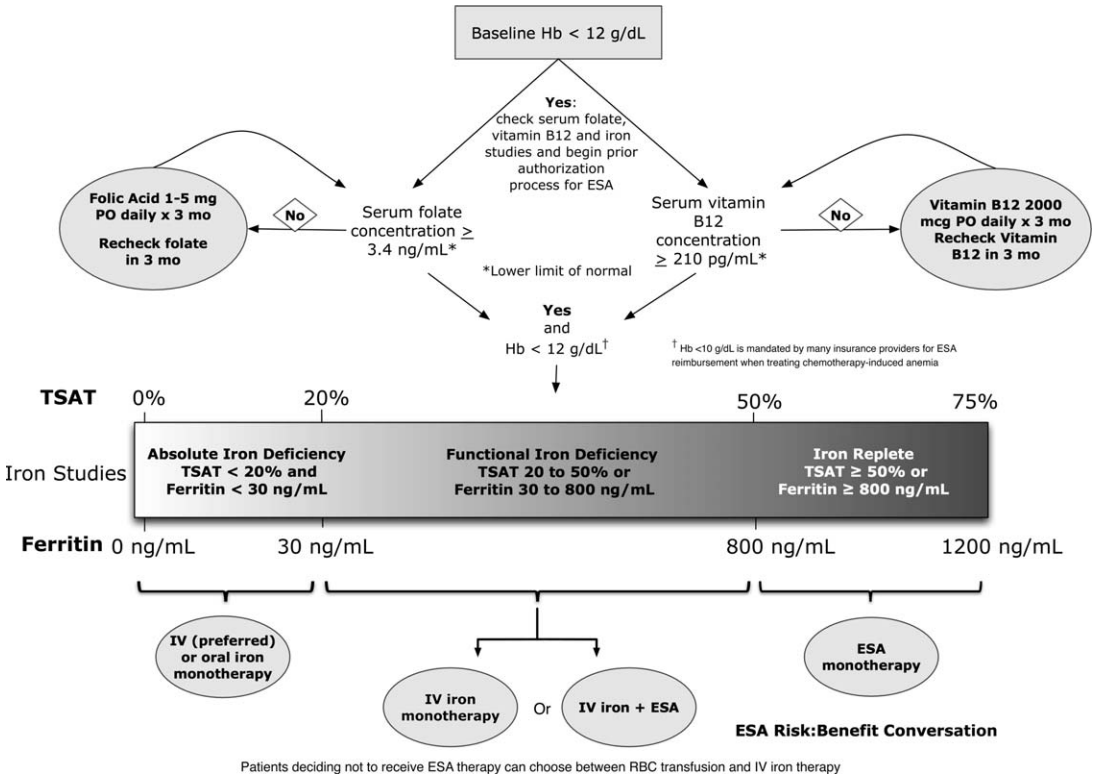

Figure 2. This figure is primarily focused on anemic cancer patients whose anemia is expected to persist greater than 3 months. Patients should be assessed for vitamin deficiency, with laboratory tests sent if required by insurance for ESA reimbursement. Vitamin deficiency should be corrected prior to treating patients with ESAs. The lower portion of the figure illustrates the spectrum of iron deficiency observed in cancer patients. Those with absolute iron deficiency should receive iron monotherapy preferably with IV iron. Iron–replete patients can be treated with ESA monotherapy. Those with functional deficiency have the option of either IV iron monotherapy (if ESAs are not to be used) or combination therapy using IV iron and an ESA. Patients considered for ESA therapy should be involved in a risk:benefifit discussion before initiation of therapy. Patients deciding not to receive ESA therapy can choose between RBC transfusion and IV iron therapy.

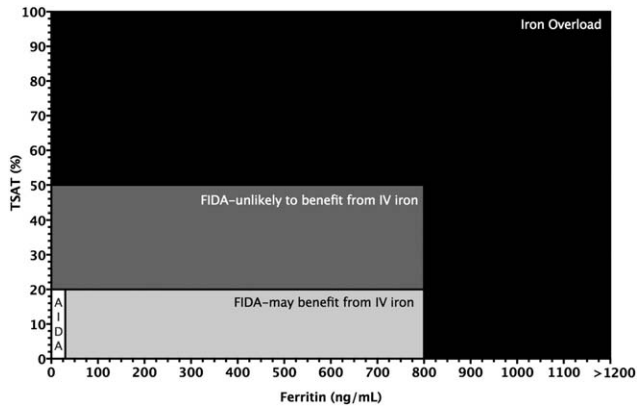

Figure 3. The relationship between TSAT, ferritin and iron stores.

cardiovascular outcomes, or sequelae from iron overload as long-term risks (beyond 6 months). As a result, although not formally studied, we prefer not to administer IV iron on the same day as anthracyclines because of the hypothetical risk that iron may potentiate cardiotoxicity [7,51–53]. Additionally, we do not administer IV iron during periods of neutropenia since the infused iron may be used by microorganisms [7,54,55], and a recent meta-analysis demonstrated a significant increased risk of infection (RR 1.33) when IV iron was compared to oral or no iron supplementation [56].

Available iron products

Oral iron is an option for AIDA (not FIDA) [45]; however, it is often not well tolerated and therefore it may take longer to correct iron deficiency [50,57]. The remainder of this review will focus on parenteral iron.

Several iron salt preparations are available for IV administration. However, only iron dextran, ferric gluconate, iron sucrose, and ferric carboxymaltose have been studied in cancer patients (Table I). High-molecular weight iron dextran (Dexferrum) is not recommended due to the increased risk for anaphylactic-type reactions, including fatalities, compared to the other iron salts, including low-molecular weight iron dextran (InFed) [58,59]. Iron dextran and ferric carboxymaltose have the advantage of administration by total-dose infusion (TDI) [60,61]. Additionally, iron sucrose and ferric carboxymaltose (≤750 mg) can be administered as IV push.

Our approach to the treatment of AIDA in patients with cancer

One benefit from classifying patients as having either AIDA or FIDA is that patients with AIDA will likely not need an ESA. We commonly treat patients identified with AIDA using a series of low-dose IV iron infusions that coincide with their clinic visits [53]. We prefer iron sucrose 200 mg given as an IV push over 2–5 min once weekly × five doses (with acetaminophen as a pre-medication) due to the ability to give as an IV push and the low adverse event rates [62,63]. We do not routinely pre-medicate with diphenhydramine due to the reported greater incidence of adverse effects [64]. We do not administer iron dextran total-dose infusion (TDI) [53] because patients with little to no storage iron consistently respond briskly to low, intermittent dosing and in our experience, patients who receive TDI have a higher rate of arthralgia and myalgia following the infusion despite premedication

with acetaminophen and corticosteroids. Additionally, ESA pharmacovigilence studies are required to assess VTE and mortality risk because of aggressive dosing used in the past. We believe IV iron studies should be held to the same standard. In addition, there are no data assessing the long-term risks such as VTE and mortality after infusing large doses of iron (>1 g) to patients with cancer [53].

Redefining functional iron deficiency

The pathophysiology of FIDA involves cytokine release associated with cancer; interleukins (IL) 1 and 6 and tumor necrosis factor (TNF) stimulate hepatic synthesis of hepcidin [35,65]. Binding of hepcidin to ferroportin in reticuloendothelial cells as well as the intestine prevents storage or dietary iron from being available for erythropoiesis [66]. This "iron block" results in functional iron deficiency. The pathophysiology of functional iron deficiency (to be defined later), or anemia of inflammation, involves multiple mechanisms, including shortened red cell survival, inhibition of erythropoiesis, suppression of renal Epo production, and sequestration of reticuloendothelial cell iron by hepcidin [67].

Inflammation associated with cancer (along with many other disorders) increases cytokines such as IL-1, tumor necrosis factor, and γ-interferon that inhibit the differentiation and survival of red cell precursors [67]. The aforementioned cytokines also suppress Epo production by the kidney, which increases apoptosis of red cell precursors in Epo-dependent stages of differentiation [68].

Hepcidin is a key regulator of iron homeostasis [69]. Hepcidin is primarily synthesized by hepatocytes, with increased synthesis occurring in response to IL-6 and other cytokines. Hepcidin acts by binding to the cellular iron export protein, ferroportin, which is expressed on the basolateral surface of enterocytes and reticuloendothelial cells [67]. Binding of hepcidin to ferroportin results in endocytosis and degradation of the transport protein, leading to limitation of gastrointestinal iron absorption and decreased export of macrophage storage iron to erythroid precursors. The end result of increased hepcidin activity is hypoferremia, low TSAT, and iron-restricted erythropoiesis [67,69]. These biochemical and cellular events explain the typical findings of iron-stained bone marrow aspirates of cancer patients showing increased storage iron yet markedly reduced-to-absent stainable iron in erythroid precursors [70].

In addition to hepcidin, another iron absorption regulatory mechanism has been described involving hypoxia inducible factor-2 (HIF-2). The HIF transcription factors mediate cellular adaptation to hypoxia, with HIF expression regulated primarily by oxygen [71]. Under iron deficient or hypoxic conditions, HIF translocates to the nucleus to activate transcription [72]. HIF-2 is now appreciated as a local regulator of enterocyte iron absorption by its trans-activation of enterocyte iron transporter genes [73]. The mechanisms by which HIF-2 may modulate intestinal iron absorption during inflammation have not yet been described.

The conundrum that clinicians face is that functional iron deficiency is a "soft diagnosis," meaning that iron studies that appear to fit the current definition of FIDA, may also fit the definition for no iron deficiency (ferritin >30 ng/mL or TSAT ≥20%), depending upon the patient-specific circumstance [7]. Ultimately, it is up to the clinician to decide whether giving iron to patients with a TSAT ≥20%, and ferritin >30 ng/mL is likely to be both safe and beneficial. For example, a cancer patient with a ferritin of 60 ng/mL may actually have AIDA, as ferritin is an acute-phase reactant. Likewise, it is under debate as to what upper treatment thresholds should be used to minimize harm while optimizing the chance for response. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guideline for anemia recommends that clinicians consider the patient's clinical status, Hb and TSAT concentration, and responsiveness (or lack thereof) to an ESA when considering IV iron for patients with a ferritin >500 ng/mL [9]. This ferritin value was not intended to serve as an absolute cut-off, but rather was intended to ensure that clinical judgment is being used due to the lack of evidence supporting or opposing an upper limit for ferritin for patients with kidney disease. At this time, the clinical trials examining the efficacy of IV iron for cancer patients have used inclusion criteria containing virtually every combination of TSAT and ferritin values. Therefore, practitioners are left with disparate data on which to support the decision to administer IV iron to patients with seemingly high TSAT and ferritin values.

Our approach to the treatment of FIDA in patients with cancer

Patients with TSATs between 20 and 50% and ferritins between 30 and 800 ng/mL can be offered IV iron with an ESA (Table III, Fig. 2). But how would one treat an anemic cancer patient with a serum ferritin of 600 ng/mL and TSAT of 16% not receiving ESA therapy? We might debate, based upon the aforementioned discussion, that the patient is iron replete and has no iron deficiency or alternatively, that this patient fits the criteria for FIDA. Intravenous iron has been shown in multiple studies to increase the Hb levels in cancer patients with both AIDA and FIDA, but all studies except one used an ESA. These studies have consistently shown a Hb response (≥2 g/dL increase) rate of approximately 10–30% when IV iron is added to ESA therapy [45,47–49]. A reduction in red cell transfusions has also been shown when IV iron is administered with an ESA [48].

If the patient with a serum ferritin of 600 ng/mL and TSAT of 16% does not receive an ESA, stimulated erythropoiesis will not occur and thus we will not create a transient state of functional iron deficiency. IV iron monotherapy (without an ESA) cannot routinely be recommended to cancer patients with FIDA as there is only one study published to date addressing this question. In a prospective, multicenter, non-randomized, observational trial, Steinmetz et al. [61] treated 619 cancer patients with ferric carboxymaltose (available in the U.S. as Injectafer®). Patients with maximal benefit had a Hb of <11 g/dL and serum ferritin <500 ng/mL, but patients with ferritin >500 ng/mL and low TSATs (mean 14.2%) also benefited. Consequently, our patient example with a serum ferritin of 600 ng/mL and TSAT of 16% could be offered IV iron monotherapy if the patient elects not to receive an ESA and the provider perceives the benefits of IV iron to outweigh the risks. Of note, unlike ESA monotherapy, IV iron monotherapy has not been evaluated regarding VTE or mortality risk.

Monitoring after IV iron

Five studies evaluating IV iron in anemic cancer patients assessed iron indices at baseline in addition to another time point after study enrollment [44–47,61]. Four studies used an ESA in conjunction with IV iron [44–47]. Two of the five studies used ferric gluconate [44,45], while the remaining four studies used either iron sucrose [46] or low molecular weight iron dextran [47], or ferric carboxymaltose [61]. The planned total doses given over the study period were as follows: 937.5 mg [44], 1,000 mg [44–47], 1,100 [46], 2,000 mg [47], and 750–1,500 mg [61]. Doses were divided into once weekly [44–46], and once every 3 weeks [47]. Four of the five studies were randomized while the fifth was an observational study [61]. Data for the randomized trials are presented in Table III.

Mean baseline TSAT and serum ferritin values for the four randomized trials ranged between 22.5–29.4% and 190–460.5 ng/mL, respectively, denoting iron "sufficiency" for most study participants despite mean baseline Hb levels ranging from 9.3 to 10.3 g/dL. All

TABLE III. Intravenous Iron Monitoring in Randomized Clinical Trials for Patients with Cancer and Receiving ESAs

	Steensma et al. [44]	Henry et al. [45]	Hedenus et al. [46]	Auerbach et al. [47]
Iron salt used	Ferric gluconate	Ferric gluconate	Iron sucrose	Low-molecular weight iron dextran
Dosing regimen	187.5 mg IV over 90 min once every 3 weeks	125 mg IV once weekly	100 mg IV every week from 0 to 6, then every other week from 8 to 14	400 mg IV every 3 weeks
Inclusion criteria	TSAT <60% Ferritin >20 ng/mL	TSAT >15 to <35% Ferritin ≥100 to <900 ng/mL	Ferritin <800 ng/mL, or stainable iron in bone marrow[a]	TSAT >15% Ferritin >10 ng/mL
Planned total dose given over study period	937.5 mg (187.5 mg IV × 5)	1,000 mg (125 mg × 8)	1,100 mg (100 mg × 10)	2,000 mg (400 mg × 5)
Number of patients enrolled in IV iron group (not control arm)	163 patients	41 patients	33 patients	116 patients
Duration of study (weeks)	16 weeks	12 weeks	16 weeks	15 weeks
Ferritin and TSAT at baseline (mean ± SD)	460.5 ng/mL ± 527, 22.5% ± 12.8	321 ng/mL ± 210, 29.4% ± 26.5	190 ng/mL, 23%[a]	301.8 ng/mL (±216.6), 27% (±18.3)
Mean change in ferritin at end of study	+265.5 ng/mL	+343.7 ng/mL SD ± 289.6 ng/mL	+~200 ng/mL[b]	+538.9 (range: 434.5–643.3 ng/mL)
Mean change in TSAT at end of study	+1.4%	−1.8% SD ± 30.5	+ ~7%	+ 6.7 (range: 2.2–11.2)
Response rates	69.5% (≥2 g/dL Hb increase above baseline or Hb ≥12 g/dL)	73% (≥2 g/dL Hb increase above baseline)	93% (≥2 g/dL Hb increase above baseline)	82% (Hb ≥11 g/dL)
Parameters for withholding IV iron during the study?	None reported	IV iron held if TSAT ≥50%, reinstated at <50%	IV iron held if ferritin >1,000 ng/mL, reinstated at <500 ng/mL	29% of patients had IV iron dose held for ferritin >1,000 ng/mL, Iron could be reinstated at <800 ng/mL
Patients receiving chemo?	Yes	Yes	No	Yes

This table includes data from the four randomized clinical trials that used IV iron in cancer patients that also assessed iron indices at baseline and at a later time.
SD = Standard deviation.
[a] Included patients with absolute iron deficiency.
[b] Exact numbers not reported, data derived from figures within the published article.

four studies reported mean change in serum ferritin and TSAT values at the end of the study.

After administering roughly 1,000 mg of iron sucrose or ferric gluconate over 5 versus 14 weeks, respectively, the mean change in ferritin did not differ substantially between studies using intermittent iron doses between 100 and 187.5 mg/dose (range: 200–343.7 ng/mL) [44–46]. In contrast, after administering 400 mg of iron dextran IV q 3 weeks × five doses, the mean change in ferritin exceeded 500 ng/mL (+538.9 ng/mL), and IV iron was withheld for 29% of patients due to exceeding a target ferritin value of 1,000 ng/mL [47]. This larger increase in ferritin was likely due to a larger average total dose of iron administered (~1,480 mg vs. 1,100 mg or less in the other studies). Table III summarizes key findings of these studies.

Regarding parameters for which to withhold iron therapy, Hedenus et al. [46] included criteria to hold IV iron if ferritin was >1,000 ng/mL, with reinstatement of therapy below 500 ng/mL; however, after enrolling patients with a mean ferritin of 190 ng/mL at baseline, no patient met this parameter after receiving a maximum of 1,000 mg of iron over a 14 week course (Table III). No clinical evidence of harm exists when serum ferritin surpasses 1,000 mg/dL due to IV iron therapy. In the absence of this information, it is up the clinician to determine frequency of monitoring in this patient population. We use a conservative serum ferritin threshold of 800 ng/mL at which to withhold IV iron therapy.

It is our practice to offer IV iron therapy to anemic cancer patients with a TSAT < 20% (Figure 3). There are insufficient data to recommend routine administration of IV iron to patients with a TSAT between 20 and 50%, without an ESA. The mean increase in TSAT at the end of the studies using either ferric gluconate or iron dextran with an ESA ranged between −1.8 and +7% (Table III). For patients receiving ESA therapy with a TSAT <50%, IV iron may be considered, but it is important to note that as the TSAT moves from 20 to 50%, the response rate decreases while time to response to IV iron increases (Figure 3) [45,61]. Therefore, for patients with baseline TSATs near the "upper limit," clinical judgment regarding the risks and benefits of IV iron is mandatory, and more frequent monitoring is recommended throughout iron therapy. Of note, all patients in the study by Hedenus et al. responded to IV iron with a Hb increase of >2 g/dL if their TSAT fell below 20% at anytime during the study [46].

Because the response to a cumulative dose of 1,000 mg of IV iron does not differ from larger doses such as those received via TDI method (Table III), we recommend not administering more than 1,000 mg in a single infusion [53]. Additionally as noted by Steinmetz et al. [61], in patients receiving a median of 1,000 mg of ferric carboxymaltose, hemoglobin levels remained stable (11–13 g/dL) in patients with elevated baseline hemoglobin (>11 g/dL). This suggests that IV iron may be self-limiting (owing to the physiologic mechanism for sequestration of excess iron) and large hemoglobin excursions above recommended thresholds may be less concerning than with ESA therapy.

Recommendations for IV iron candidates and iron monitoring

Anemic patients should be classified as either iron replete, having AIDA, or FIDA. Patients with AIDA will not need an ESA. After a baseline assessment, patients who are cured of their disease may still need ongoing iron monitoring despite the limited duration of chemotherapy. This is because in patients with AIDA, 1,000 mg of IV iron is adequate to correct anemia; however, this dose may not be adequate to completely replete iron storage pools. For most patients with FIDA, we believe that after receipt of 1,000 mg of IV iron, additional supplementation is unlikely to offer benefit. Patients with relapsed or metastatic disease may benefit from ongoing monitoring regarding guidance on continued dosing; however, studies are needed

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to determine the most appropriate intervals for repeating TSAT and ferritin testing. Clinicians should consider repeating iron studies 3–4 weeks after the last dose of iron has been administered if the MCV falls below 80 fL. Although not validated in clinical trials, adjunct tests such as the content of reticulocyte hemoglobin (CHr) and visualization of a peripheral smear for hypochromic red cells may help to determine when repeat dosing of iron may be required [74,75]. Although their usage is rapidly increasing for other disease states, these tests may not be readily available to all clinicians.

RBC Transfusion Versus ESAs

Patients who are not candidates for ESA therapy

ESAs are not currently recommended for anemic cancer patients who are not receiving myelosuppressive chemotherapy or who have curable disease [6,7]. Options for this group include red cell transfusion and intravenous iron. Transfusion is an acceptable treatment option for anemic cancer patients, especially those requiring rapid improvement of hemoglobin (Hb) levels. One unit of packed red cells is estimated to increase Hb levels of an average-sized adult (who is not bleeding) by ~1 g/dL [76].

The benefits and risks of red cell transfusion have been well studied. Analysis of a large healthcare database found that red cell transfusion in cancer patients was associated with increased risks of arterial and venous thrombosis as well as increased mortality risk [77]. Decreased cancer patient survival was also reported in surgical patients who received red cell transfusion [78].

Transfusion is also associated with other risks, including volume overload, transmission of viral or bacterial infection, iron overload, and transfusion-related acute lung injury [7,78]. Given the risks of red cell transfusion and the limited blood supply that could be adversely impacted by increasing use of red cells [79], we suggest that anemic cancer patients whose anemia requires therapy be presented with a benefit-risk discussion of treating either with red cell transfusion versus intravenous iron with or without ESAs, depending upon whether the patient is receiving palliative chemotherapy or not [7].

A misconception by many clinicians is that since packed red cells contain 147–278 mg of iron per unit of blood, red cell transfusions reverse iron deficiency. However, the average lifespan of a transfused red cell is approximately 100–110 days, and therefore the iron that will eventually be phagocytosed from transfused red cells is not immediately available for erythropoiesis [80]. Additionally in anemia of inflammation, iron may take even longer to be recycled as a result of being sequestered in macrophages. Therefore, administration of iron after red cell transfusion may prove useful in the 90 days following a transfusion, if the anemia stemmed from iron deficiency. Pre-transfusion iron indices are recommended for this reason, among others.

Candidates for ESA therapy

We currently consider ESA therapy for patients receiving palliative, myelosuppressive chemotherapy with a Hb <10 g/dL and without absolute iron deficiency [7]. It is important to note that although newer targeted therapies such as sunitinib, erlotinib, or trastuzumab commonly contribute to anemia, the ESA package labels do not mention whether these are included under the definition of myelosuppressive agents [20]. When dosing ESA therapy, we prefer subcutaneous (SQ) over the IV route, because doses given IV are cleared from the plasma more quickly and are therefore less effective [81–84]. In our practice, we routinely use epoetin or darbepoetin extended interval dosing, such as every other week or every 3 weeks to coincide with patients' chemotherapy regimens (Table I). Because of the diagnosis-related group (DRG) coverage, we frequently divide the dosing into weekly intervals while patients are hospitalized, with resumption of their maintenance dosing and frequency when they become ambulatory.

The FDA-approved label for ESAs was changed in 2008 to mandate that ESAs are "not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure." Therefore, for patients receiving palliative chemotherapy, anemia treatment options would include ESAs, IV iron, red cell transfusion, or no therapy. Patients receiving curative chemotherapy should only be offered the options of red cell transfusion, IV iron, or no therapy. This FDA restriction was based on clinical trial data available at that time that indicated decreased cancer patient survival and loco-regional control in patients receiving ESAs. However, to this date, there have been no clinical trials performed that stratified patients based on treatment intent (curative vs. palliative). This issue is further complicated by the recognition that patient treatment goals (intent of treatment) require clinical judgment.

How we conduct an ESA risk:benefit conversation

This risk:benefit conversation is mandated by the FDA risk evaluation and mitigation strategy for ESAs. The program dictates that a frank and thorough discussion take place with the patient regarding the benefits and untoward effects of ESAs, including an increased risk of VTE as well as the possibility of drug-induced disease progression. This conversation can be difficult as some patients with incurable malignancies are not always aware of the gravity of their situation. From our experience, roughly 50% of our patients choose not to receive an ESA, despite meeting clinical and laboratory criteria, due to fear of progressive disease. Also, the line between "curable" and "incurable" can be gray at best. As we are proponents of these agents, when used within approved indications, we advocate the early implementation of anemia therapy as cancer-related fatigue is nearly ubiquitous in late stages of disease and often is the most distressing symptom patients experience [85].

Monitoring after ESA administration

Both the ASH/ASCO and NCCN guidelines on ESA therapy in cancer patients follow the FDA recommendations [6,7]. Hemoglobin trends should initially be monitored weekly regardless of the ESA type or frequency chosen. If no Hb response (<1 g/dL increase above baseline) occurs after 4 weeks for epoetin or 6 weeks for darbepoetin, dose escalation is recommended. If the Hb increases by >1 g/dL in any 2-week period, or if the "Hb target is reached to avoid transfusion," dose reduction (25% for epoetin, 40% for darbepoetin) or frequency augmentation (our preference) is recommended.

ESA response rates

The percentage of cancer patients "responding" to ESAs varies widely in clinical trials, from 45 to ~90% [46,86]. The definition of an ESA response varies in clinical trials including: a hemoglobin increase of 1 or 2 g/dL from baseline, a ≥ 2 g/dL increase in Hb values from baseline, or a reduction in RBC transfusions (Table III). In our practice, if transfusion requirements have clearly diminished as a result of ESA use in patients actively receiving chemotherapy, we consider these patients responders and do not discontinue the ESA if the Hb fails to rise by 1 g/dL above baseline unless myelosuppressive treatment has ceased. Factors affecting response rates include co-administration of IV iron, baseline Hb, age, type of cancer therapy, and duration of therapy [87]. Across most studies, administering an ESA alone yields response rates of 55–65% [87,88], and in patients also receiving IV iron, the response rate increases to approximately 80% [44–47].

ESA hyporesponsiveness

Currently, the best predictor of ESA response is a rapid rise in Hb values [89]. In patients not responding to ESA therapy after dose

escalation and 6–8 weeks of continuous ESA therapy, it is unlikely that insufficient ESA dosing is responsible for the lack of response. Auerbach et al. demonstrated in patients receiving 300 or 500 mcg of darbepoetin every 3 weeks no statistical difference in achieved target Hb (75 and 78%, respectively) or the median time to target hemoglobin (10 vs. 8 weeks, respectively) [47]. To our knowledge, no study has prospectively assessed the benefit of systematic dosing increases of ESAs for lack of response, and only one study has allowed increased doses for lack of response; however, they did not report whether this intervention was beneficial [90]. Therefore, we recommend correcting underlying factors of persistent anemia and optimizing iron therapy rather than ESA therapy, as functional iron deficiency is likely a contributing factor. Evidence for this can be seen in the study by Steinmetz et al., where the Hb increase was 1.4 g/dl using IV iron alone versus a 1.6 g/dL increase in the IV iron + ESA arm [61]. Interestingly, 64% of patients receiving IV iron alone achieved a Hb level above 10 g/dL, a level not permitted by CMS. Other major contributing factors to persistent anemia despite ESA therapy include rate of blood loss, either through direct effects of cancer invasion, thrombocytopenia-related bleeding, or frequent phlebotomy. For this reason, ESAs are not indicated during episodes of bleeding as they are indicated for treating decreased red cell production, not blood loss. Additionally, we recommend cautious use of ESAs in patients whose transfusion requirements have not decreased or who have failed to realize an increase in hemoglobin of greater than 1 g/dL after 6–8 weeks of dosing. Deleterious effects of ESAs, while originally thought to be due to increased blood viscosity (with or without subsequent platelet activation [91,92]) or agonistic effect on tumor cell epo receptors, may actually be due to unopposed circulating plasma erythropoietin [92,93]. This hypothesis may help to explain reasons for increased VTE and mortality risk in patients with Hb values in the low or normal range, who received higher doses due to "targeting" a higher Hb value.

How long after chemotherapy should patients continue to receive an ESA?

In general, ESA therapy should be discontinued when the chemotherapy course has been completed (roughly 6–8 weeks after the last dose of chemotherapy), or if there is no Hb response after 8 weeks of treatment. Little information is known about the length of time for erythroid progenitor recovery after myelosuppressive chemotherapy. The myelosuppressive potential of chemotherapy and its half-life likely play a role, in addition to the cumulative effect of chemotherapy after multiple cycles. Although the NCCN guidelines suggest a time frame of 6 weeks after the last dose of chemotherapy, it is clear that stem cell transplant patients often benefit from continuing an ESA for longer durations [94,95]. When treating solid tumor malignancies, it is unlikely that chemotherapy contributes to suppression of hematopoiesis 2 months after the last dose [96].

The package inserts for epoetin alfa and darbepoetin alfa do not address this issue, nor does the REMS program. Based upon animal model data, the effects of erythroid suppression from chemotherapy should resolve after 6–8 weeks, with the rate of hematopoiesis compensating for reduced production to avoid transfusion [96]. However, other causes of anemia may persist (iron deficiency, or CKD) and the clinician may inadvertently continue an ESA if these other causes of anemia are not recognized. Therefore, we recommend ongoing evaluation, even after the cessation of chemotherapy, to determine the optimal timing of discontinuation.

Practical Implications

CMS regulations

The target Hb, as listed in the package inserts of ESAs, is the "lowest to prevent the need for RBC transfusion." Although the clinical target is purposefully vague to allow clinicians to predict trends based upon the potential extent of bone marrow suppression of the chemotherapy regimen, the Hb target may be dictated by the patient's insurance coverage. The majority of our patients are insured by CMS, and therefore the threshold at which we are permitted to begin ESA therapy is <10 g/dL. Additionally, we are not permitted to target a Hb above 10 g/dL. There are exceptions to this rule, of course. For patients who are younger than 65 years, we obtain prior authorization from their primary insurance to determine the allowable beginning and target Hb for their specific situation and whether we are required to draw B-vitamin levels.

ESAs for cancer patients with history of VTE

A consistently demonstrated risk of ESA therapy in cancer patients is thromboembolism. The 2012 Cochrane review update on ESA safety surveyed 91 trials with over 20,000 patients and identified a relative risk for thromboembolism of 1.52 in ESA-treated patients [87]. The number needed to harm (NNTH) depends upon the baseline risk of VTE. As the VTE risk increases from 2 to 10% the NNTH decreases from 96 to 19 patients treated with an ESA [87]. When using ESA therapy, variables not demonstrating evidence for an increased risk of VTE include the baseline Hb level, type of malignancy, duration of treatment, type of cancer therapy, and iron supplementation. However, this meta-analysis did not include the achieved Hb level, which in other studies has correlated with an increased risk. ESA-associated thrombosis risk has been particularly noted in multiple myeloma patients receiving thalidomide and dexamethasone, and also ESA-treated cancer patients with a Hb increase >2 g/dL per month, or those whose target Hb exceeds 13 g/dL [97]. There are no clinical trials addressing the question of how to manage cancer patients with prior thrombosis who are being considered for ESA therapy. For those patients who are currently anticoagulated, we recommend continuing their anticoagulation during the period of ESA therapy. Further studies are warranted to determine the role of primary VTE prophylaxis in patients with high baseline risk for VTE who are considering ESA treatment.

Using CKD as a diagnosis to prescribe an ESA

The target Hb threshold for CKD patients insured under CMS is 12 g/dL versus 10 g/dL if using a diagnosis of CIA. Anemic patients qualify for an ESA when they have reached stage III CKD (an estimated creatinine clearance of less than 60 mL/min normalized to a body surface area of 1.73 based on the MDRD estimated glomerular filtration rate equation). Roughly 40% of our anemic cancer patients will qualify for an ESA at some point after their cancer diagnosis simply by virtue of their renal function [98]. For example, an anemic 64-year-old male, 5'10", 73 kg patient would qualify for an ESA if his serum creatinine was 1.23 mg/dL (for ≥3 months). However, it may be inappropriate to use an ESA in this setting if patients are not receiving chemotherapy [99,100]. In a study by Smith et al. [99], a deleterious effect of darbepoetin 6.75 mcg/kg given every 4 weeks was demonstrated in cancer patients with a median age of 64 years who were not receiving chemotherapy. Therefore, if the decision to treat anemia "secondary to CKD" is made, CKD-approved starting doses (epoetin: 50–100 units/kg SQ TIW, darbepoetin: 0.45 mcg SQ IV q 4 weeks) of ESAs are recommended (Table I) if myelosuppressive chemotherapy is not given [99]. We recognize the dose may need to be escalated or the frequency may need to be decreased, however, if contemplating ESA dose escalation beyond 0.75 mcg/kg SQ every 2 weeks (hemodialysis dosing), other causes of anemia should be pursued with the potential discontinuation of the ESA.

Conclusion

The appropriate sub-classification of CRA will help clinicians develop a systematic approach to managing treatment options for cancer patients. The assessment of iron status should be considered for symptomatic patients with CRA, while nutritional deficiency assessment should be reserved for patients with clinical signs or symptoms of deficiency or when insurance mandates testing prior to ESA therapy. As the role of IV iron

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monotherapy is evolving, long-term safety data will be required before this practice becomes the cornerstone of treatment for patients with CRA.

Author Contributions

JG, DS, and GR each participated in writing, editing, and have all approved the final draft of the manuscript.

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