HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

Cancer-Related Anemia

Contributors:

Shruti Chaturvedi, MD
Clinical Fellow, Division of Hematology and Oncology, Vanderbilt-Ingram Cancer Center/Vanderbilt University Medical Center, Nashville, TN

Michael R. Savona, MD
Associate Professor of Medicine, Division of Hematology and Oncology, Vanderbilt-Ingram Cancer Center/Vanderbilt University Medical Center, Nashville, TN

Table of Contents

Introduction 1
Etiology and Pathogenesis 1
Therapy 2
Conclusions and Future Directions 7
Board Review Questions 8
References 8

Cancer-Related Anemia

Shruti Chaturvedi, MD, and Michael R. Savona, MD

INTRODUCTION

Anemia occurs in more than half of patients with cancer[1] and is associated with worse performance status, quality of life, and survival.[2,3] Anemia is often attributed to the effects of chemotherapy; however, a 2004 European Cancer Anemia Survey reported that 39% of patients with cancer were anemic *prior* to starting chemotherapy[4] and the incidence of anemia may be as high as 90% in patients on chemotherapy.[5] The pathogenesis of cancer-related anemia is multifactorial; it can be a direct result of cancer invading the bone marrow, or result from the effects of radiation, chemotherapy-induced anemia, chronic renal disease, and cancer-related inflammation leading to functional iron deficiency anemia.[6,7]

Treatment of cancer-related anemia has been controversial. Previously, blood transfusion and erythropoiesis-stimulating agents (ESAs) were considered standard and effective options for the treatment of anemia in cancer patients.[8] Subsequent clinical trial data raised concerns about ESA safety, specifically, thrombosis risk and patient survival in solid malignancies.[9–12] This led to warnings issued by the regulatory authorities and restrictions on the use of these products.[8,13] Later clinical trials designed to address mortality related to ESA therapy in patients with chemotherapy-induced anemia were less concerning.[14,15] At the same time new data emerged regarding the safety and efficacy of intravenous iron in anemic patients with cancer,[16–22] and parenteral iron therapy made its way into practice guidelines.[6,13] Taken together, our understanding of anemia in cancer and the decision-making and therapeutic methods when treating it have become more complicated. This article discusses the etiology of cancer-associated anemia and current evidence guiding its management.

ETIOLOGY AND PATHOGENESIS

Anemia in patients with cancer may be directly related to the effects of cancer, including bone marrow invasion, blood loss from direct tumor invasion, and inflammation-induced functional iron deficiency anemia (FIDA); chemotherapy- and radiation-induced anemia; or anemia secondary to other patient factors including nutritional deficiencies and renal impairment.[6,7]

EFFECTS OF CANCER ON BONE MARROW

Tumor cells can directly invade the bone marrow and cause anemia. Hematologic malignancies frequently present with hyperproliferation of blasts in the bone marrow, which can lead to anemia by suppressing normal erythropoiesis and preventing the interaction between bone marrow stromal cells and erythroid precursors that is essential for differentiation and proliferation.[23,24] Erythroid production is further hindered in the presence of bone marrow fibrosis seen in some metastatic solid tumors and a variety of hematologic malignancies, including myeloproliferative disorders (primary myelofibrosis, chronic myelogenous leukemia), myelodysplastic/myeloproliferative disorders (chronic myelomonocytic leukemia, refractory anemia with ringed sideroblasts and thrombocytosis, atypical chronic myeloid leukemia), some acute leukemias (acute megakaryoblastic leukemia, acute pan-myelosis with fibrosis), and some myelodysplastic syndromes.[25] Many of these conditions are associated with abnormalities in number and function of megakaryocytes and platelets. Cytokines derived from these cells appear to be necessary but not sufficient for the development of fibrosis. Recent studies have also underlined the role of transforming growth factor–β, a potent stimulant of fibroblast collagen synthesis, in the pathologic deposition of bone marrow stromal fibers.[26]

Pure red cell aplasia may develop due to tumor-derived cytokines in patients with thymoma, leukemia, or lymphoma, or rarely secondary to the formation of anti-erythropoietin antibodies after exogenous erythropoietin (Epo) use.[27–29]

Malignancy-associated inflammation leads to the release of cytokines such as interleukin (IL)-1, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α that are important mediators of cancer-related anemia. First, these inflammatory cytokines suppress erythro-

poietin production by the kidney and thus inhibit the differentiation and survival of erythroid precursors in the bone marrow.[30] Second, they lead to functional iron deficiency, which is an important cause of anemia in patients with cancer. Increased levels of the cytokines IL-1, IL-6, and TNF-α stimulate the synthesis of hepcidin, a key regulator of iron homeostasis.[31–33] Hepcidin binds to ferroportin, a cellular iron export protein on the basolateral surface of enterocytes and reticuloendothelial cells, and causes endocytosis and degradation of the transport protein, in turn leading to a "block" in enteral iron absorption and decreased export of storage iron from macrophages to erythroid precursors in the bone marrow.[31–33] The end result of these processes is iron-restricted erythropoiesis, hypoferremia, and low transferrin saturation. This absorption block explains why oral iron supplementation is frequently ineffective in patients with anemia of cancer.[34]

Hypoxia-inducible factor 2 (HIF-2) has been identified as another regulator of iron absorption that activates transcription of enterocyte iron transporter genes under iron deficient or hypoxic conditions, although its role in cancer- and inflammation-related anemia is yet to be elucidated.[35,36] Hypoxia-inducible factor 1-α (HIF-α) is a related transcription factor that regulates erythropoietin production in response to hypoxia.[37] Its exact role in anemia of inflammation remains to be defined.

Cancer patients may develop autoimmune hemolysis (AIHA) or Evans syndrome (AIHA and immune-mediated thrombocytopenia), which is most commonly seen in lymphoproliferative disorders such as chronic lymphocytic leukemia or lymphomas.[38] Hypersplenism with sequestration of hematopoietic cells occurs in myeloproliferative neoplasms and lymphoid malignancies. Tumor-related mutations in c-kit (CD117), or its inhibition by targeted therapies, reduce erythropoiesis by inhibiting the erythropoietin receptor and c-kit signal transduction pathways.[39,40]

CHEMOTHERAPY-RELATED ANEMIA

Several chemotherapeutic agents induce anemia by impairing hematopoiesis. This occurs most frequently in patients receiving highly myelosuppressive chemotherapy.[41] The myelosuppressive effect of cytotoxic chemotherapy is often cumulative, thus leading to increasing incidence and severity of anemia with consecutive cycles of chemotherapy.[4] In addition, nephrotoxicity from agents such as cisplatin can lead to the persistence of anemia through decreased renal erythropoietin production.[42] Drugs such as fludarabine can cause anemia by directly inducing hemolysis and Evans syndrome.[43] Finally, some drugs such as gemcitabine, cyclosporine, or tacrolimus can cause microangiopathic hemolytic anemia.[44]

OTHER HOST FACTORS CAUSING ANEMIA

Chronic kidney disease, either preexisting or as a result of tumor invasion or chemotherapy, may be present in a significant number of patients[45] and is more common among older patients with diminished creatinine clearances in the setting of rapid swings in metabolic activity and volume shifts with new cancer diagnoses and therapy. While absolute iron deficiency is present in 29% to 60% of patients with cancer,[46] vitamin B_{12} and folate deficiencies are less common.[7] Chronic inflammatory diseases, acute and chronic blood loss, chronic infections, and primary autoimmune hemolytic anemia are other factors that may contribute to anemia in patients with cancer.

THERAPY

ERYTHROPOIETIN-STIMULATING AGENTS

Erythropoietin, a glycosylated globulin protein synthesized in the interstitial fibroblasts and the proximal tubular cells of the kidney, was first described by Jacobson and colleagues in 1957.[47] It binds to erythropoietin receptors (Epo-R) on red blood cell precursors in the bone marrow and promotes their erythroproliferation and erythrodifferentiation and inhibits apoptosis of erythroid progenitor cells.[48] The downstream effects of Epo-R activation occur through the JAK-STAT signal transduction pathways.[49] In addition to binding to erythrocyte precursors, Epo-Rs are present on normal endothelial cells, neurons, and myocardial cells[50–52] where they promote cell repair and inhibit apoptosis.[52,53] There have been concerns that Epo signaling could lead to increased survival and resistance to apoptosis in cancer cells. Indeed, in vitro studies have shown that Epo-induced signal transduction can increase cell proliferation,[54] induce resistance to apoptosis,[55] and even promote tumor cell migration.[56] In addition, tumor hypoxia, which is clearly implicated in tumor progression, is associated with upregulation of HIF-1α and may be associated with increased expression of Epo-R[57] and resistance to hypoxia-mediated apoptosis.[58,59] However, these effects may have been exaggerated in laboratory models of tumor progression. Moreover, the presence of Epo-R messenger RNA in cancer cells has not been shown to correlate with surface expression of Epo-R.[60,61] The clinical relevance of these extrahematopoietic effects of Epo in human tumors has been evaluated in clinical trials as described below.

The gene for Epo was cloned in 1984,[47] and recombinant Epo for the treatment of anemia became available in 1989.[62] Three ESAs are used clinically in the United States and Western Europe—epoetin-alfa, epoetin-beta, and darbepoetin-alfa, which is an N-glycosylated recombinant Epo with a longer half life. Equivalent doses of these agents have identical effects on transfusion requirements, overall survival, quality of life, tumor progression, and venous thromboembolic events,[63] and therefore they have not been differentiated in the discussion that follows.

ESAs were originally approved for use in patients with chronic kidney disease (CKD) who had reduced endogenous Epo. In 1993, the U.S. Food and Drug Administration (FDA) approved their use in patients with cancer receiving chemotherapy with the primary goal of reducing the number of red blood cell transfusions. A series of subsequent analyses revealed transfusion reductions and improvement in hemoglobin levels with ESAs for patients with anemia that arises during or shortly after myelotoxic chemotherapy.[64–69] A 2002 meta-analysis of these studies indicated that ESAs decreased transfusion requirements in 68% of patients with cancer-associated anemia.[70] As a result of these findings, the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) first published a joint evidence-based clinical practice guideline for the use of epoetin in adults with chemotherapy-induced anemia in 2002.[70]

A post-marketing study (N93-004) was initiated at the time of approval of epoetin for chemotherapy-induced anemia.[71] The primary objective was to determine the effect of epoetin on tumor response in small cell lung cancer in patients receiving treatment with etoposide and cisplatin. This study was discontinued because of slow accrual, but an intention-to-treat analysis of 224 patients showed no significant difference in overall response rates. A second trial in 2001 with 375 patients indicated a 1.4-fold increased survival rate in epoetin-treated anemic patients with cancer undergoing chemotherapy.[72] Although not powered to evaluate differences in survival, these trials opened the door for other studies examining the effect of ESAs on tumor progression and survival.

These trials raised awareness of issues regarding thrombosis and disease progression risks associated with ESAs, and led to concern for a potential deleterious effect on mortality.[73–85] In 2003, the 2 initial studies that aimed to measure differences in survival with ESA therapy were halted early or concluded with adverse effects on survival.[73,74] The BEST trial included 939 women with metastatic breast cancer who were randomized to placebo versus ESA to maintain hemoglobin between 10 and 12 g/dL for 1 year. The primary outcome was overall survival. This study was terminated early due to the results of an interim analysis that indicated worse overall survival in the treatment arm (70% versus 76%, $P = 0.01$).[73] In the ENHANCE trial, 351 patients with head and neck cancer were randomly assigned to receive placebo or epoetin for the duration of radiation therapy. Epoetin corrected anemia but led to inferior locoregional progression-free survival (relative risk [RR] 1.62, 95% confidence interval [CI] 1.05 to 1.84, $P = 0.02$).[74] Both these studies have been criticized for various reasons including unbalanced treatment arms, unreasonably high target hemoglobin levels, and continued cigarette smoking among patients on the test arm of the ENHANCE study, and higher than recommended doses of epoetin-alfa (40,000 IU/week in the BEST trial and 300 IU/kg in the ENHANCE trial). However, subsequent randomized studies showed shortened survival or increased risk of tumor progression in patients with gynecological cancers, non-small cell lung cancer, and various lymphoproliferative malignancies or mixed nonmyeloid cancer.[80–83] Three additional trials evaluating the efficacy and safety of ESAs in patients with small cell lung cancer, gastric cancer, and cervical cancer had to be halted prematurely because of an alarming fourfold increase in the rate of venous thromboembolic events in the ESA arms.[72,86,87] These concerns prompted the Oncologic Drug Advisory Committee and subsequently the FDA to mandate label changes alerting prescribing physicians to the risks of tumor progression and shortened survival.[84,85]

It should be noted that all of the studies that showed decreased overall survival with ESAs utilized a hemoglobin goal of greater than 12 g/dL, and several of these used unapproved dosing regimens. No studies have evaluated the dose-intensity of ESA treatment as a risk factor for tumor response or survival. In 2007, the FDA issued 2 black box warnings on ESA safety based on survival data and also recommended limiting the use of ESAs to patients with cancer receiving myelosuppressive chemotherapy. In 2008, the hemoglobin threshold to initiate treatment was lowered to less than 10 g/dL. In 2008, a multicenter, randomized, placebo-controlled study evaluating the efficacy and safety of darbepoetin in patients with active cancer who were not receiving chemotherapy demonstrated shortened survival in the ESA arm.[88] Thus, anemia of cancer not associated with chemotherapy or myeloablative radiation is listed as a contraindication to ESA use, with the exception of myelodysplastic syndromes where it actually improves outcomes.[89,90] The 2010 ASH/ASCO guidelines and the National Comprehensive Cancer Network (NCCN)

guidelines issued in 2012 recommend that ESA therapy should be limited to anemia patients with cancer who are receiving palliative chemotherapy. The lowest dose of ESAs needed to avoid transfusions should be used and therapy should be discontinued after completion of chemotherapy when anemia resolves (usually 6 to 8 weeks after the last cycle).[6,13] Physicians should have a frank and detailed discussion with patients regarding the benefits and risks of ESA therapy, including increased thromboembolic risk and, with exception of myelodysplastic syndrome, possible ESA-induced disease progression.

ESAs in Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) present a unique situation wherein dyserythropoiesis is inherent to disease pathogenesis and causes severe and persistent anemia that is directly linked to organ failure and mortality. As juxtaposed to the solid tumor ESA trials, early trials looking at ESA use in MDS yielded overwhelmingly positive results. MDS comprises a heterogeneous group of clonal diseases that can be stratified into low-, intermediate-, and high-risk disease by the International Prognostic Scoring System.[91] Due to the high rate of progression to acute leukemia in intermediate-2 and high-risk MDS, treatment is focused on modifying the disease process with chemotherapy and hematopoietic cell transplantation. Patients with lower risk MDS, however, are often treated successfully for many years with ESAs and granulocyte-colony stimulating factors to decrease transfusion requirements and infectious risk.[89,91] This approach reduces need for transfusions and decreases the incidence of iron overload syndromes, a major cause of morbidity in transfusion-dependent low-risk MDS.[92] A 2008 French study reported a striking survival advantage in patients with low-risk MDS treated with ESAs as compared with an untreated historical control cohort (64% versus 39%, $P > 0.01$). Significantly higher response rates were observed with less than 10% blasts, low- and intermediate-1 risk disease, red blood cell transfusion independence, and serum Epo level less than 200 IU/L.[93] Interestingly, when ESA responders and nonresponders were compared, responders had a 5-year survival of nearly 80% versus around 50% in nonresponders.[93] This observation suggests a need for the assessment of response to epoetin and emphasizes the need to understand the mechanisms of response and resistance to epoetin.

ESA Responsiveness

Different studies have used different definitions for response to ESA therapy, including a hemoglobin increase of 1 or 2 g/dL, a reduction in red blood cell transfusions, or transfusion independence. The best predictor of a response to ESAs is a rapid rise in hemoglobin level and a decrease in transfusion requirements. In general, ESA alone yields response rates of 55% to 65%,[94] which increase to approximately 70% to 90% when used along with parenteral iron.[13–19] Lack of response to ESAs after dose escalation and 6 to 8 weeks of continuous therapy is unlikely to be due to insufficient dosing. For example, in a study by Auerbach et al, in patients receiving 3 weekly doses of darbepoetin 300 µg or 500 µg, there was no difference in response rates (75% versus 78%) and median time to response (10 weeks versus 8 weeks, respectively).[19]

Systematic increases in ESA dosing for lack of response have not been studied. On the other hand, deleterious effects of ESA therapy, including venous thromboembolism, and cardiovascular risk may be related to higher hemoglobin targets.[95,96] ESA hyporesponsiveness may be related to alteration of the signal transduction pathway downstream to the Epo-R. For example, alterations in the JAK-STAT pathways,[49] TNF-α-induced triggering of NF-KB and GATA-2, and inhibition of GATA-1 pathways are believed to be involved in poor response to epoetin.[97,98] Poor response to ESA therapy can also be related to continued blood loss due to tumor invasion or thrombocytopenia, repeated phlebotomy, or nutritional deficiencies including absolute or functional iron deficiency.

Another, less common, cause for nonresponsiveness to epoetin is pure red cell aplasia (PRCA), or anemia due to ESA-neutralizing antibodies. Between 1998 and 2004, 197 cases of epoetin-induced PRCA were reported. More than 90% of these cases occurred in patients with CKD treated with Eprex, an epoetin-alfa product used outside the United States.[27] Since 2004, another 30 cases of PRCA have been reported with epoetin-alfa and darbepoetin alfa. These cases were attributed to reactions with stabilizing agents, leachate from rubber stoppers, and aggregation from tungsten. Interventions against these causes decreased the incidence of epoetin-related PRCA by 83%,[99] but PRCA is likely still underreported. The FDA recommends that any patient who develops sudden loss of response to an ESA should be evaluated for the presence of neutralizing antibodies to epoetin. All ESAs should be permanently discontinued in patients with antibody-mediated anemia.[6]

IRON REPLACEMENT THERAPY

Until approximately 2008, treatment of anemia and cancer was limited to red blood cell transfusions and ESAs. However, iron deficiency has been reported in 29%

Table 1. Summary of Parenteral Iron Formulations

Preparation	Dosing and Administration*	Frequency (based on 1000 mg total dose)	Immunogenicity
Iron dextran (Dexferrum, INFeD)	100–250 mg intravenously over 5 minutes, or TDI over several hours	Repeat weekly until 1 g is administered Repeat TDI every 4 weeks if total dose > 1 g	High (0.6%–1.7%). Test dose (25 mg slow IV push) is *required*. Higher with HMW iron dextran (Dexferrum) than LMW iron dextran (INFeD)
Iron sucrose (Venofer)	100–200 mg IV push over 2 to 5 minutes, or infusion over 1 hour	Repeat dosing every 1 to 4 weeks	Lowest (0.002%). Can be used safely in patients with hypersensitivity to iron dextran. Test dose recommended if drug allergies present
Ferric gluconate (Ferrlecit)	125 mg intravenously over 60 minutes	Repeat weekly for 8 doses	Low (0.04%) Test dose recommended if drug allergies present
Ferric carboxymaltose (Injectafer)	750 mg IV push over 15 minutes	Repeat after at least 7 days if needed (maximum dose 1500 mg elemental iron per course)	Low (<1%) Limited experience in cancer-related anemia

HMW = high-molecular weight; IV = intravenous; LMW = low-molecular weight; TDI = total dose infusion.

*Iron dosages are estimates but vary depending on level of anemia, iron deficiency, and body mass.

Information based on Rodgers et al,[6] Gilreath et al,[7] and Silverstein and Rodgers.[100]

to 60% of patients with cancer in 5 separate studies.[46] Also, 63% of anemic cancer patients were reported to have transferrin saturation and ferritin levels lower than those needed to prevent iron-restricted erythropoiesis. Iron studies are recommended in order to exclude a preexisting iron deficiency before starting an ESA because ESA-stimulated erythropoiesis requires bioavailable iron.

Patients can be classified as iron replete, having absolute iron deficiency (ferritin <30 ng/dL, transferrin saturation <15%), or having functional iron deficiency (ferritin 30–800 ng/dL and transferrin saturation <20%).[6,7] Patients with absolute iron deficiency may be treated with iron supplementation only, while those with functional iron deficiency should receive ESAs along with parenteral iron.[6] Although oral iron may be used in patients with absolute iron deficiency, multiple studies have demonstrated that it is less effective than parenteral iron in patients with cancer (and functional iron deficiency).[16–22] In a prospective, multicenter, open-label study, 157 patients with chemotherapy-induced anemia who were receiving ESA therapy were randomized to no iron, oral iron, or parenteral iron. Patients who received parenteral iron had greater increments in hemoglobin levels than those receiving oral iron or no iron.[19] A second study by Henry et al in 187 patients with chemotherapy-induced anemia also reported a higher hemoglobin response rate with intravenous iron compared to oral or no iron.[21] In 2008, Bastit et al demonstrated that intravenous iron use was associated with reduced red blood cell transfusions.[17] Although multiple subsequent studies have demonstrated that intravenous iron enhances the hematopoietic response to ESAs, it has not been shown that iron supplementation decreases ESA dose. Mean baseline hemoglobin levels in these studies ranged from 9.3 to 10.3 g/dL, while mean baseline ferritin and transferrin saturation ranged between 190 and 460.5 ng/dL and 22.5% to 29.4%, respectively. Cumulative iron dose was between 750 and 2000 mg. Patients who received higher total iron doses had hematologic responses no different from those who received lower doses, although they were more likely to have iron therapy withheld because they exceeded the target ferritin level of 1000 ng/dL. Current guidelines recommend withholding iron infusions when ferritin is ≥800 ng/dL and restarting when ferritin drops to 500 ng/dL.[5,7,13]

Several intravenous iron preparations are available. Of these, only iron dextran, iron sucrose, ferric gluconate, and iron carboxymaltose have been studied in patients with cancer.[13–19] Recommended doses and regimens of these preparations are summarized in **Table 1**.[6,7,100] Iron sucrose and iron carboxymaltose can be administered by intravenous push dosing, while iron

dextran and iron carboxymaltose may be administered by total dose infusion;[100] while convenient, total dose infusion is not favored because patients with low iron stores respond well to low intermittent dosing, and also because there is a higher incidence of arthralgias and myalgias with total dose infusion despite appropriate premedication.[101] There is no difference in hemoglobin response with intermittent dosing or total dose infusion. Iron dextran has also been associated with a higher incidence of hypersensitivity reactions (0.6%–1.7%), including anaphylaxis, than ferric gluconate (0.04%) and iron sucrose (0.002%).[100]

Other common adverse effects after parenteral iron administration include flushing, nausea, vomiting, hypotension, hypertension, pruritus, nausea, vomiting, and diarrhea.[100] A meta-analysis demonstrated an increased risk of infection (RR 1.33) with parenteral iron,[102] and therefore it is reasonable to avoid iron infusions during neutropenia or acute infections. Importantly, none of the studies discussed above have addressed the effect of parenteral iron on mortality, infection, venous thromboembolism, or cardiovascular morbidity from iron overload. Interestingly, Steinmetz at al noted that in patients receiving a median dose of 1000 mg of ferric carboxymaltose, hemoglobin levels remained stable (11–13 g/dL) in those who had an elevated baseline hemoglobin level (>11 g/dL).[103] This suggests that parenteral iron therapy is self-limiting due to physiologic iron sequestration and that large hemoglobin excursions may be of less concern than excessive ESA therapy, although there are legitimate concerns regarding the effects of iron overload.

RED BLOOD CELL TRANSFUSIONS

Red blood cell transfusion was the earliest treatment available for anemia in patients with cancer. It still has a role in patients who require a rapid improvement in hemoglobin levels and patients who are not candidates for ESA therapy, such as those receiving chemotherapy with curative intent.[6] It is often utilized in patients with MDS, where dyserythropoiesis is central to disease pathogenesis. One unit of packed red blood cells typically raises hemoglobin level by approximately 1 g/dL in an average-size adult who does not have concurrent blood loss.[104] Although one unit of packed red cells contains between 147 and 278 mg of iron and eventually provides an iron load, it is not immediately available for erythropoiesis since the life span of a red blood cell is 100 to 120 days and the iron it contains will not be immediately available. Also, iron recycling is impaired and may take even longer in patients with anemia of inflammation (or FIDA).[105]

Transfusion is associated with several risks including uncommon risks of transmission of bacterial or viral infections, major transfusion reactions, transfusion-related acute lung injury, as well as common consequences of volume overload, minor transfusion reactions, and iron overload.[106] Khorana et al reported an increased risk of venous thromboembolism (odds ratio [OR] 1.60, 95% CI 1.53 to 1.67), arterial thrombosis (OR 1.53, 95% CI 1.29 to 1.38), and mortality (OR 1.34, 95% CI 1.29 to 1.38) associated with packed blood cell transfusions in patients with cancer.[107] However, these risks are typically outweighed by perfusion and oxygenation when indications for red cell transfusion are stringently applied.

Transfusion-related iron overload is an important cumulative adverse effect that is of special concern in patients with transfusion-dependent, low-risk MDS. The longer survival of low- and intermediate-1 risk MDS (by IPSS classification) can potentially lead to exposure to a greater number of transfusions over a prolonged period, placing them at higher risk of iron overload than patients with higher-risk MDS who have relatively shorter survival.[92] Iron overload in MDS begins even before transfusion dependence because of downregulation of hepcidin synthesis due to ineffective erythropoiesis that leads to increased enteral iron absorption.[108] However, the major cause of iron overload is still transfusional iron as evidenced by serum ferritin levels in patients with MDS at diagnosis and prior to starting transfusion therapy which are usually between 400 and 1000 ng/dL.[109] Iron cannot be actively excreted, so it accumulates, first in the reticuloendothelial cells and then in the parenchymal cells of the heart, liver, and endocrine organs, leading to impaired function.[110] A retrospective analysis of a U.S. database reported that cardiac events, liver disease, and diabetes mellitus were more frequent in MDS patients receiving blood transfusions.[111] Iron overload is independently associated with poorer survival in patients with MDS.[112,113] Serum ferritin is an independent prognostic factor in MDS, and over a threshold of 1000 ng/dL it has a dose-dependent effect on overall survival.[112]

Iron chelation therapy (ICT) facilitates negative iron balance and should be considered in patients with lower-risk MDS with reasonable life expectancy, and really in any appropriate cancer patient with more than 20 to 25 blood transfusions in their lifetime and serum ferritin higher than a certain threshold, usually 1000 ng/dL.[114] ICT has several potential benefits. It is expected to improve cardiac and hepatic function. Ironically, ICT has also been reported to improve hematologic responses with increased hemoglobin,

Table 2. Summary of Treatment Options for Cancer- and Chemotherapy-Associated Anemia

	ESAs	Parenteral Iron	Red Blood Cell Transfusion
Indications	Chemotherapy-associated anemia in patients being treated with palliative intent Low and intermediate-1 risk MDS	Absolute iron deficiency Along with ESAs in functional iron deficiency	Rapid improvement in hemoglobin needed Patients receiving chemotherapy with curative intent Active bleeding
Benefits	Avoids transfusions and iron overload Gradual improvement in fatigue Improved survival in MDS	Improved hemoglobin response rate Transfusion avoidance	Rapid improvement in perfusion, oxygenation, and symptoms
Risks	Increased risk of thrombosis, tumor progression, and decreased survival	Hypersensitivity reactions including anaphylaxis (increasingly uncommon) Flushing, nausea, vomiting, hypotension, hypertension, pruritus, nausea, vomiting, and diarrhea Arthralgias and myalgias	Transfusion reactions (hemolytic, nonhemolytic, febrile, acute lung injury) Transfusion-associated circulatory overload Transmission of infections (rare) Iron overload Increased thrombotic events

ESA = erythropoiesis-stimulating agent; MDS = myelodysplastic syndromes.

diminished transfusion requirements, and even transfusion independence in a proportion of patients with MDS.[115–118] Of the 341 patients with MDS included in the EPIC study of 1744 patients with various transfusion-dependent anemias, 22.6% demonstrated an erythropoietic response and half of these had a hemoglobin increment of 1.5 g/dL or more.[119] Retrospective studies have also indicated that ICT has a favorable impact on overall survival,[120–122] although these studies are fraught with bias since patients with higher expected survival were more likely to be started on ICT. This bias may be overcome by the ongoing TELESTO study (NCT 00940602), a prospective, randomized, placebo-controlled trial looking at event-free survival with ICT in MDS.

Three iron chelators are available: deferoxamine, deferiprone, and deferasirox. Deferoxamine was the first agent approved almost 3 decades ago and must be administered exclusively parenterally because of poor enteral absorption.[114] Deferiprone is orally bioavailable due to its smaller size and lipid solubility but must be taken 3 times a day. Painful joint swelling is a commonly reported adverse effect but does not usually necessitate cessation of treatment. Deferiprone has been associated with agranulocytosis that is particularly worrisome in patients with MDS who may have preexisting neutropenia.[114,123] Deferasirox is the newest and most commonly used oral iron chelator that can be dosed once a day.[124] Diarrhea, abdominal cramping, rash, and rise in serum creatinine are the major side effects.

Table 2 summarizes treatment options for anemia in patients with cancer.

CONCLUSION AND FUTURE DIRECTIONS

Anemia in patients with cancer is a multifactorial problem, with cancer-related inflammation, chemotherapy, and nutritional factors affecting its severity. A detailed assessment of etiology should be pursued to enable clinicians to provide individualized treatment. Identifiable causes should be addressed if possible. Patients can be classified iron replete, having absolute iron deficiency, or having functional iron deficiency. There are high response rates to ESAs in cancer-related anemia, and these are augmented by the addition of parenteral iron to overcome functional iron deficiency. ESAs are approved for use in patients with chemotherapy-induced anemia receiving palliative chemotherapy, but not those receiving chemotherapy with curative intent or no chemotherapy. ESAs carry potential risks such as venous thromboembolism, tumor progression, and worsened survival, and a frank risk-benefit discussion with the patient is warranted before initiating ESA therapy. On the contrary, ESA therapy is especially useful in patients with MDS, where it improves survival

and decreases transfusion requirements. Iron overload secondary to red cell transfusions is a major cause of morbidity in patients with MDS. ICT may help mitigate this effect in selected patients.

Newer agents targeting hepcidin are being evaluated for the treatment of inflammatory anemia. For example, tocilizumab (anti-IL-6 receptor antibody) has been shown to downregulate hepcidin and improve anemia of inflammation in multicentric Castleman disease and rheumatoid arthritis.[125,126] Alternative approaches aimed at pharmacological control of hepcidin expression and targeting different regulatory steps have been attempted. They include hepcidin-sequestering agents (antibodies, anticalins, and aptamers) inhibitors of BMP/SMAD, IL-6/STAT3 pathway or hepcidin transduction (siRNA/shRNA), and ferroportin stabilizers.[127] These may lead to expansion of our arsenal against anemia in cancer.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic. Go to www.turner-white.com and select Hematology from the drop-down menu of specialties.

REFERENCES

1. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med 2004;116:11–26.
2. Steinmetz T, Totzke U, Schweigert M, et al. A prospective observational study of anaemia management in cancer patients - results from the German Cancer Anaemia Registry. Eur J Cancer Care (Engl) 2011;20:493–502.
3. Waters JS, O'Brien ME, Ashley S. Management of anemia in patients receiving chemotherapy. J Clin Oncol 2002;20:601–3.
4. Ludwig H, Van Belle S, Barrett Lee P, et al. The European Cancer Anemia Survey (ECAS): A large, multinational, prospective survey defining the prevalence, incidence and treatment of anemia in cancer patients. J Natnl Compr Canc Netw 2008;6:577–84.
5. Tas F, Eralp Y, Basaran M, et al. Anaemia in oncology practice: relation to diseases and their therapies. Am J Clin Oncol 2004; 2 Suppl 1: 11–26.
6. Rodgers GM, Becker PS, Blinder M, et al. Cancer and chemotherapy induced anemia. J Natl Compr Canc Netw 2012;10:628–53.
7. Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Hematol 2014;89:203–12.
8. Rodgers GM. A perspective on the evolution of management of cancer and chemotherapy induced anemia. J Natl Compr Canc Netw 2012;10:434–7
9. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006;98:708–14.
10. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol 2005;23:5960–72.
11. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomized double-blind, placebo-controlled trial. Lancet 2003;362:1255–60.
12. Hess G, Nordyke RJ, Hill J, et al. Effect of reimbursement changes on erythropoiesis stimulating agent utilization and transfusions. Am J Hematol 2010;85:838–43.
13. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guidelines on the use of epoietin and darbepoetin in adult patients with cancer. J Clin Oncol 2010;28: 4996–5010.
14. Rodgers GM. A perspective on the evolution of management of cancer- and chemotherapy-induced anemia. J Natl Compr Canc Netw 2012;10:434–7.
15. Engert A, Josting A, Haverkamp H, et al. Epoetin alfa in patients with advanced-stage Hodgkin's lymphoma: Results of the randomized placebo-controlled GHSG HD15EPO trial. J Clin Oncol 2010;28:2239–45
16. Auerbach M, Silberstein PT, Webb RT, et al. Darbepoetin alfa 300 or 500 µg once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. Am J Hematol 2010;85:655–63.
17. Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alfa administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol 2008;26:1611–8.
18. Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. J Clin Oncol 2008;26:1619–25.
19. Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: A multicenter, open-label, randomized trial. J Clin Oncol 2004;22:1301–7.
20. Steensma DP, Sloan JA, Dakhil SR, et al. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. J Clin Oncol 2011;29:97–105.
21. Henry DH, Dahl NV, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 2007;12:231–42.
22. Hedenus M, Birgegård G, Näsman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin re-

sponse and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: A randomized multicenter study. Leukemia 2007;21:627–32.
23. Gordon MY, Kearney L, Hibbin JA. Effects of human marrow stromal cells on proliferation by human granulocytic (GM-CFC), erythroid (BFU-E) and mixed (Mix-CFC) colony-forming cells. Br J Haematol 1983;53:317–25.
24. Kobune M, Kawano Y, Kato J, et al. Expansion of CD34+ cells on telomerized human stromal cells without losing erythroid-differentiation potential in a serum-free condition. Int J Hematol 2005;81:18–25.
25. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rational and important changes. Blood 2008;1145:937–51.
26. Della Porta MG, Malcovati L. Myelodysplastic syndromes with bone marrow fibrosis. Haematologica 2011;96:180–3.
27. Bennett CL, Luminari S, Nissenson AR, et al. Pure-red cell aplasia and epoietin therapy. N Engl J Med 2004;351: 1403–8.
28. Thompson CA, Steensma DP. Pure red cell aplasia associated with thymoma: Clinical insights from a 50-year single-institution experience. Br J Haematol 2006;135:405–7.
29. Wang SA, Yue G, Hutchinson L, et al. Myelodysplastic syndrome with pure red cell aplasia shows characteristic clinicopathological features and clonal T-cell expansion. Br J Haematol 2007;138:271–5.
30. Miller CB, Jones RJ, Piantadosi S, et al. Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med 1990; 322:1689–92.
31. Lee P, Peng H, Gelbart T, et al. Regulation of hepcidin transcription by interleukin-1 and interleukin-6. Proc Natl Acad Sci USA 2005;102:1906–10.
32. Ganz T, Nemeth E. Hepcidin and iron homeostasis. Biochem Biophys Acta 2012;1823:1434–43.
33. Deicher R, Horl WH. New insights into the regulation of iron homeostasis. Eur J Clin Invest 2006;36:301–9.
34. Henry DH, Dahl NV, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 2007;12:231–42.
35. Wenger RH, Stiehl DP, Camenisch G. Integration of oxygen signaling at the consensus HRE. Sci STKE 2005;2005:re12.
36. Mastrogiannaki M, Matak P, Peyssonnaux C. The gut in iron homeostasis: Role of HIF-2 under normal and pathological conditions. Blood 2013;122:885–92.
37. Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci USA. 1995;92:5510–14.
38. Mauro FR, Foa R, Cerretti R, et al. Autoimmune hemolytic anemia in chronic lymphocytic leukemia: Clinical, therapeutic, and prognostic features. Blood 2000;95:2786–92.
39. Munugalavadla V, Kapur R. Role of c-Kit and erythropoietin receptor in erythropoiesis. Crit Rev Oncol Hematol 2005;54:63–75.
40. Barni S, Cabiddu M, Guarneri P, et al. The risk for anemia with targeted therapies for solid tumors. Oncologist 2012;17:715–24
41. Wilson J, Yao G, Rafferty J, et al. A systematic review and economic evaluation of epoetin alpha epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess 2007;11:1–202, III–IV.
42. Groopman J, Itri L. Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst 1999;91:1616–34.
43. Calixto R, Ostronoff F, Ostronoff M, et al. Immune hemolysis after fludarabine-based reduced intensity conditioning and allogeneic PBSC transplantation for CML with minor ABO incompatibility. Ann Hematol 2012;91:295–7.
44. Al-Nouri ZL, Reese JA, Terrell DR, et al. Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood 2014 Nov 20 pii: blood-2014-11-611335. [Epub ahead of print]
45. Bennett CL, Becker PS, Kraut EH, et al. Intersecting guidelines: Administering erythropoiesis stimulating agents to chronic kidney disease patients with cancer. Semin Dial 2009; 22:1–4.
46. Aapro M, Jelkmann W, Constantinescu SN, Leyland-Jones B. Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer. Br J Cancer 2012; 106:1249–58.
47. Jacobson LO, Goldwasser E, Fried W, Plzak L. Role of the kidney in erythropoiesis. Nature 1957;179:633–4.
48. Ebert BL, Bunn HF. Regulation of the erythropoietin gene. Blood 1999;94:1864–77.
49. Witthuhn BA, Quelle FW, Silvennoinen O, et al. JAK2 associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin. Cell 1993;74:227–36.
50. Anagnostou A, Lee ES, Kessimian N, et al. Erythropoietin has a mitogenic and positive chemotactic effect on endothelial cells. Proc Natl Acad Sci USA 1990;87:5978–82.
51. Masuda S, Nagao M, Takahata K, et al. Functional erythropoietin receptor of the cells with neural characteristics: comparison with receptor properties of erythroid cells. J Biol Chem 1993;268:11208–16.
52. Bianchi R, Buyukakilli B, Brines M, et al. Erythropoietin both protects from and reverses experimental diabetic neuropathy. Proc Natl Acad Sci USA 2004;101:823–8.
53. Calvillo L, Latini R, Kajstura J, et al. Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. Proc Natl Acad Sci USA 2003;100:4802–6.
54. Feldman L, Wang Y, Rhim JS, et al. Erythropoietin stimulates growth and STAT5 phosphorylation in human prostate epithelial and prostate cancer cells. Prostate 2006;66:135–45.
55. Dunlop EA, Percy MJ, Boland MP, et al. Induction of signalling in non-erythroid cells by pharmacological levels of erythropoietin. Neurodegener Dis 2006;3:94–100.
56. Lester RD, Jo M, Campana WM, et al. Erythropoietin promotes MCF-7 breast cancer cell migration by an ERK/

mitogen-activated protein kinase-dependent pathway and is primarily responsible for the increase in migration observed in hypoxia. J Biol Chem 2005;280:39273–7.
57. Fyles AW, Milosevic M, Wong R, et al. Oxygenation predicts radiation response and survival in patients with cervix cancer. Radiother Oncol 1998;48:149–56.
58. Yasuda Y, Musha T, Tanaka H, et al. Inhibition of erythropoietin signalling destroys xenografts of ovarian and uterine cancers in nude mice. Br J Cancer 2001;84:836–43.
59. Westenfelder C, Baranowski RL. Erythropoietin stimulates proliferation of human renal carcinoma cells. Kidney Int 2000;58:647–57.
60. Dagnon K, Pacary E, Commo F, et al. Expression of erythropoietin and erythropoietin receptor in non-small cell lung carcinomas. Clin Cancer Res 2005;11:993–9.
61. Sinclair AM, Busse LNR. Epo receptor transcription is not elevated nor predictive of surface expression in human tumor cells. Proc Am Assoc Cancer Res 2005;46:5457a.
62. Lee-Huang S. Cloning and expression of human erythropoietin cDNA in Escherichia coli. Proc Natl Acad Sci USA 1984;81:2708–12.
63. Seidenfeld J, Piper M, Bohlius J, et al. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. Comparative Effectiveness Review No. 3. Agency for Healthcare Research and Quality; 2006.
64. Bohlius J, Langensiepen S, Schwarzer G, et al. Erythropoietin for patients with malignant disease. Cochrane Database Syst Rev 2004;3:CD003407.
65. Engert A. Recombinant human erythropoietin in oncology: Current status and further developments. Ann Oncol 2005;16:1584–95.
66. Seidenfeld J, Aronson N, Piper M, et al. Uses of epoetin for anemia in oncology. Evid Rep Technol Assess (Summ) 2001;29:1–8.
67. Seidenfeld J, Piper M, Aronson N. Systematic review of controlled trials on erythropoietin to support evidence-based guidelines. Oncology (Williston Park) 2002(suppl 10);6:171–88.
68. Seidenfeld J, Piper M, Flamm C, et al. Epoetin treatment of anemia associated with cancer therapy: A systematic review and meta-analysis of controlled clinical trials. J Natl Cancer Inst 2001;93:1204–14.
69. Waltzman RJ. Treatment of chemotherapy- related anemia with erythropoietic agents: Current approaches and new paradigms. Semin Hematol 2004;4:9–16.
70. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 2002;20:4083–107.
71. FDA Oncologic Drugs Advisory Committee (ODAC). Briefing Document: Safety concerns associated with Aranesp (darbepoetin alfa) Amgen, Inc. and Procrit (epoetin alfa) Ortho Biotech, L.P., for treatment of anemia associated with cancer chemotherapy. May 4, 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2_04.pdf.
72. Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double blind, placebo-controlled trial. J Clin Oncol 2001;2865–74.
73. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: A survival study. J Clin Oncol 2005;23:5960–72.
74. Henke M, Laszig R, Rübe C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1255–60.
75. Be CL, Henke M, Lai SY. Erythropoiesis stimulating agents in the treatment of cancer-associated anemia (Reply). JAMA 2008;300:2855–7.
76. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: A meta-analysis of randomised trials. Lancet 2009;373:1532–42.
77. Bohlius J, Wilson J, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2006;3:CD003407.
78. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including9353 patients. J Natl Cancer Inst 2006;98:708–14.
79. Glaspy J, Smith R, Aapro M, et al. Results from a phase III, randomized, double-blind, placebo-controlled controlled study of darbepoetin alfa for the treatment of anemia in patients not receiving chemotherapy or radiotherapy. Presented at the 98th Annual Meeting of the American Association for Cancer Research, Los Angeles, CA, April 14–28, 2007.
80. Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. Br J Haematol 2003;122:394–403.
81. Overgaard J, Hoff C, San Hansen H. Randomized study of the importance of novel erythropoiesis stimulating protein (Aranesp) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC): The Danish Head and Neck Cancer Group DAHANCA. Eur J Cancer 2007;7(suppl 5):Abstract 6LB.
82. Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with diseaserelated anemia. J Clin Oncol 2007;25:1027–32.
83. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 2008;108:317–25.
84. US Food and Drug Administration. FDA news release: FDA receives new data on risks of anemia drugs consistent with

previous data on tumor growth and death. www.fda.gov/News Events/Newsroom/PressAnnouncements/2008/ucm116830.htm
85. 25. US Food and Drug Administration. FDA briefing document, May 10, 2007, Oncologic Drugs Advisory Committee. Continuing reassessment of the risks of erythropoiesis-stimulating agents (ESAs) administered for the treatment of anemia associated with cancer chemotherapy. www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf
86. Vadhan-Raj SS, Crane C, Buesos-Ramos C, et al. Randomized, doubleblind, placebo-controlled trial of epoetin alfa (Procrit) in patients with rectal and gastric cancer undergoing chemo-radiotherapy (CT/RT) followed by surgery: early termination of the trial due to increased incidence of thrombo-embolic events (TEE). Blood 2004;104:797a.
87. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 2007;108:317–25.
88. Smith RE Jr, Aapro MS, Ludwig H, et al. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. J Clin Oncol 2008;26;1040–50.
89. Hellstrom-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood 1998;92:68–75.
90. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validate decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol 2003;120:1037–46.
91. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079–88.
92. Shenoy N, Vallumsetla N, Rachmilewitz E, et al. Impact of iron overload and potential benefit from iron chelation in low risk myelodysplastic syndrome. Blood 2014;124:873–81.
93. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 2008;111:574–82.
94. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012;12:CD003407.
95. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–98.
96. Drüeke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–84.
97. Morceau F, Dicato M, Diederich M. Pro-inflammatory cytokine mediated anemia: regarding molecular mechanisms of erythropoiesis. Mediators Inflamm 2009;2009:405016.
98. Ohneda K, Yammamoto M. Roles of hematopoietic transcription factors GATA-1 and GATA-2 in the development of red blood cell lineage. Acta Haematol 2002;108:237–45.
99. McKoy J, Stonecash R, Cournoyer D, et al. Epoietin-associated pure red cell aplasia: past, present and future considerations. Transfusion 2008;48:1754–62.
100. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol 2004;76:74–8.
101. Gilreath JA, Stenehjem D, Rodgers GM. Total dose iron dextran infusion in cancer patients: Is it SaFe21? J Natl Compr Canc Netw 2012;10:669–76.
102. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: Systematic review and meta-analysis of randomized clinical trials. BMJ 2013;347:f4822.
103. Steinmetz T, Tschechne B, Harlin O, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy associated anaemia. Ann Oncol 2013;24:475–82.
104. Wiesen AR, Hospenthal DR, Byrd JC, et al. Equilibration of hemoglobin concentration after transfusion in medical inpatients not actively bleeding. Ann Intern Med 1994;121:278-80.
105. Luten M, Roerdinkholder-Stoelwinder B, Schaap NPM, et al. Survival of red blood cells after transfusion: A comparison between red cells concentrates of different storage periods. Transfusion 2008;48:1478–85.
106. Spivak JL, Gascon P, Ludwig H. Anemia management in oncology and hematology. Oncologist 2009;14(Suppl 1): 43–56.
107. Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis and mortality in hospitalized patients with cancer. Arch Intern Med 2008;168:2377–81.
108. Santini V, Girelli D, Sanna A, et al. Hepcidin levels and their determinants in different types of myelodysplastic syndromes. PLoS ONE 2011;6:e23109.
109. Gattermann N. Clinical consequences of iron overload in myelodysplastic syndromes and treatment with chelators. Hematol Oncol Clin North Am 2005;19(Suppl. 1):13–7.
110. Siah CW, Ombiga J, Adams LA, et al. Normal iron metabolism and the pathophysiology of iron overload disorders. Clin Biochem Rev 2006;27:5–16.
111. Goldberg SL, Chen E, Corral M, et al. Incidence and clinical complications of myelodysplastic syndromes among United States medicare beneficiaries. J Clin Oncol 2010;28:2847–52.
112. Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica 2006;91:1588–90.
113. Sanz G, Nomdedeu B, Such E, et al. Independent impact of iron overload and transfusion dependency on survival and leukemic evolution in patients with myelodysplastic syndrome. Blood 2008;112:640.
114. Steensma DP, Gattermann N. When is iron overload deleterious, and when and how should iron chelation therapy be

administered in myelodysplastic syndromes? Best Pract Res Clin Haematol 2013;26:431–44.
115. Messa E, Cilloni D, Messa F, et al. Deferasirox treatment improved the hemoglobin level and decreased transfusion requirements in four patients with the myelodysplastic syndrome and primary myelofibrosis. Acta Haematol 2008;120:70–4.
116. Capalbo P, Spinosa G, Franzese MG, et al. Early deferasirox treatment in a patient with myelodysplastic syndrome results in a long-term reduction in transfusion requirements. Acta Haematol 2009;121:19–20.
117. Okabe H, Suzuki T, Omori T, et al. Hematopoietic recovery after administration of deferasirox for transfusional iron overload in a case of myelodysplastic syndrome. Rinsho Ketsueki 2009;50:1626–9.
118. Badawi MA, Vickars L, Chase JM. Red blood cell transfusion independence following the initiation of iron chelation therapy in myelodysplastic syndrome. Adv Hematol 2010;2010:164045.
119. Gattermann N, Finelli C, Della Porta M, et al. Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes. Haematologica 2012;97:1364–71.
120. Leitch HA, Leger CS, Goodman TA, et al. Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. Clin Leuk 2008;2:205–11.
121. Rose C, Brechignac S, Vassilief D, et al. Does iron chelation therapy improve survival in regularly transfused lower risk MDS patients? A multicenter study by the GFM. Leuk Res 2010;34:864–70.
122. Neukirchen J, Fox F, Kundgen A, et al. Improved survival in MDS patients receiving iron chelation therapy – a matched pair analysis of 188 patients from the Dusseldorf MDS registry. Leuk Res 2012;36:1067–70.
123. Gattermann N. Pathophysiological and clinical aspects of iron chelation therapy in MDS. Curr Pharm Des 2012;18:3222–34.
124. Breccia M, Alimena G. Efficacy and safety of deferasirox in myelodysplastic syndromes.Ann Hematol 2013;92:863–70.
125. Song SN, Tomosugi N, Kawabata H, et al. Down-regulation of hepcidin resulting from long-term treatment with an anti-IL-6 receptor antibody (tocilizumab) improves anemia of inflammation in multicentric Castleman disease. Blood 2010;116:3627–34.
126. Hashimoto M, Fujii T, Hamaguchi M, et al. Increase of hemoglobin levels by anti-IL-6 receptor antibody (tocilizumab) in rheumatoid arthritis. PLoS One 2014;9:e98202.
127. Poli M, Asperti M, Ruzzenenti P, et al. Hepcidin antagonists for potential treatments of disorders with hepcidin excess. Front Pharmacol 2014;5:86.