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REVIEW ARTICLE

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Anemia management in cancer patients with chronic kidney disease

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Abstract

Cancer and kidney disease are linked by causality and comorbidities. Observational data show an increased risk of malignancy as renal function declines. Erythropoietin stimulating agents (ESAs), which are the cornerstone therapy for anemia patients with chronic kidney disease and cancer, are associated with increased risks for cancer, cancer-related mortality, progression of disease, and thromboembolic events. This article examines the recently published guidelines for ESA use in cancer patients from the American Society of Clinical Oncology and American Society of Hematology and attempts to contextualize them to the care of patients with coexistent CKD, cancer, and anemia.

Cancer and kidney disease are linked by causality and comorbidities. More than 50% of patients with a diagnosis of cancer or ESRD also have anemia. Patients with cancer can develop CKD due to direct and indirect effects of the tumor on the kidney itself or from treatment-related toxicity. Erythropoietin-stimulating agents (ESAs) form the cornerstone for treatment of anemia caused by CKD or cancer therapy. Since they were first introduced in 1989, ESAs have significantly decreased transfusion dependence and the attendant risks for infection, iron overload, and presensitization and they have improved anemia-related symptoms and quality of life measure in patients with either CKD or cancer.

Over a decade after their introduction, data linking ESA use with negative clinical outcomes began to emerge. Prior to 1998, placebo-controlled studies of CKD patients were designed to evaluate the short-term safety and efficacy of erythropoietin (EPO); most targeted a Hg of 9.5-12 g/dL. Although not designed to evaluate cardiovascular endpoints, these studies demonstrated an increased risk for hypertension and thrombosis in the ESA-treated groups. Between 1998 and 2008 a shift occurred during which larger studies, principally sponsored by ESA manufacturers, compared higher versus lower Hg targets (9-12 g/dL vs 12-15 g/dL). A meta-analyses of ESA trials in CKD patients revealed that higher Hg targets were associated with increased risk for stroke, hypertension, and vascular access thrombosis across all stages of CKD.[1] ESA use also corresponded with a higher odds ratio (OR) for developing a new cancer,[2] and in patients with cancer, ESA use correlated with tumor growth, shorter progression-free survival (PFS),[3] and an increased risk of mortality.[4-6]

Observational data show an increased risk of malignancy in ESRD patients.[7] Secondary analysis of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)[8] demonstrated that patients with a previous malignancy who received darbepoetin to target a Hg of 13 g/dL had a significantly higher risk of dying from cancer than those in the placebo group. Because patients with cancer are excluded from CKD trials, and patients with CKD are excluded from cancer trials, there are no well-designed clinical studies that examine the relationship between ESA exposure in patients with CKD and the risk for new or recurrent malignancy. The Surveillance of Epoetin-Adverse Events of Stroke and Cancer (SEASCAN)[9] study, designed to examine the risk for cancer with ESA use, found no significant association between ESA treatment and malignancy. Regrettably, follow-up was limited to 6 months, making it difficult to draw any substantive conclusions.

Currently, there are no clear and specific guidelines for ESA use in the management of anemia in patients with both CKD and a current or past diagnosis of cancer. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO)[10] gave a grade IB recommendation ("we recommend" with "moderate" quality of evidence") that ESAs be used with "great caution" in all CKD patients with active malignancy, particularly when cure is the anticipated outcome. For

CKD patients with a past history of malignancy, KDIGO made a similar but weaker recommendation (grade 2C: "we suggest" with "low" quality of evidence). In June 2019, the American Society of Clinical Oncology (ASCO) and the American College of Hematology (ASH) updated their clinical practice guidelines for the management of cancer-associated anemia (Table 1).[11] The objective of this article was to review some of the clinical data upon which these guidelines were established. I hope that this background information will enable clinicians to make more informed decisions in the application of these guidelines to their specific patients.

In vitro and in vivo data indicate that ESAs promote tumorigenesis and angiogenesis. Like endogenous EPO, ESAs bind to and activate extracellular EPO receptors (EpoR) on erythroid progenitor cells in the bone marrow. When ESAs bind the EpoR on the cell membrane, there is autophosphorylation of Janus-activated 2 (JAK2) kinase, a transducer of cancer cell signaling. In turn, JAK2 kinases phosphorylate tyrosine residues on the intracellular domains of the EpoR. The intracellular domains act as docking sites for various cytoplasmic signaling proteins such as signal transducer and activator of transcription (STAT) 5, protein kinase B (AKT) and extracellular signal-regulated kinase (ERK) 1/2. Stimulation of these proteins can lead to cellular differentiation, proliferation, and anti-apoptosis.[12] EPO binding to the EpoR also induces nuclear translocation of nuclear factor-κB (NF- κB), which may induce anti apoptotic gene transcription.[13]

TABLE 1 Summary of the American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update

Before offering an ESA, conduct a history, physical exam and diagnostic tests to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy.
ESAs should not be offered to patients with chemotherapy associated anemia whose cancer treatment is curative in intent.
ESAs may be offered to patients with chemotherapy associated anemia whose cancer treatment in not curative in intent and whose Hg is <10 g/dL. Depending on the severity of anemia and clinical circumstances, RBC transfusion is also an option.
ESAs should not be offered to patients with nonchemotherapy associated anemia. One exception is that ESAs may be offered to patients with lower risk MDS and a serum EPO level <500 IU/L
For patients with MM, NHL or CLL, clinicians should observe the hematologic response before considering an ESA.
All ESA (epoetin beta and alfa, biosimilar epoetin alfa) are considered equivalent with regard to safety and efficacy.
ESAs increase the risk for thromboembolism. Physicians must weight the risks of thromboembolism and use caution and clinical judgment when considering ESA use.
When starting or modifying ESA doses, follow the FDA guidelines.
ESAs may be used to target the lowest Hg concentration needed to avoid or reduce the need for RBC transfusions.
ESAs should be discontinued in patients who do not respond within 6-8 wk, as evidenced by a rise in Hg of less than 1-2 g/dL or no decrease in transfusion requirement. Patients who do not respond to ESA should be reevaluated for underlying tumor progression, iron deficiency or other etiologies.
Iron replacement may be used to improve Hg response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency

Abbreviations: CLL, Chronic Lymphocytic Leukemia; EPO, Epoetin; ESA, Erythropoietin Stimulating Agents; MDS, Myelodysplastic Syndrome; MM, Multiple Myeloma; NHL, Non Hodgkin Lymphoma.

Multiple tumor types express the EpoR, including lung, breast, colon, gastric, squamous cell of the head and neck, and uterine cancer.[14-19] A possible role for JAK-STAT signaling in cancer progression was demonstrated in studies on cell lines from squamous cell carcinoma of the head and neck. EPO promoted tumor invasion was subsequently blocked by a JAK inhibitor as well as in a cell line with a STAT5A mutation.[18] Tumor migration in a breast cancer cell line was increased through the activation of EPO/EpoR induced ERK activation. This effect was mitigated in the presence of soluble EpoR or anti-Epo antibodies.[20] In human melanoma cells, EPO activated the AKT signaling pathway and increased tumor cell survival. Tumor cell viability was diminished following cotreatment with an AKT inhibitor.[21]

While these data suggest a protumorigenic role for ESAs, these pleiotropic molecules do not always behave as anticipated and can be difficult to properly study with currently available methods. A major limitation of current studies is that the commercially available antibodies used to target the EpoR are nonspecific and overlap with other proteins. Heat shock protein (HSP)70 is one such overlapping protein and high expression of HSP-70 is itself linked to poorer prognosis, more aggressive disease and resistance to chemotherapy.[22] Importantly, there may be considerable reporting biases since most of the negative studies for evidence of functional EpoR expression in tumor cells were funded by ESA manufacturers, whereas positive studies come from nonfunded academic researchers.[23-26]

Based on the results of the in vitro and in vivo studies which demonstrated that the EPO-EpoR complex promotes differentiation of normal endothelial cells into vascular tubes and new blood vessel formation,[17] researchers hypothesized that ESAs' proangiogenic effects and their capacity to increase Hg would increase delivery of chemotherapy, decrease the hypoxic tumoral milieu, and thereby improve patient outcomes. Consequently, several clinical cancer trials were designed to target Hg levels above 12 g/dL. Contrary to the expected outcomes, ESA use in several of these trials demonstrated greater locoregional progression, shorter PFS, lower odds of survival, shorter disease-free survival and increased death.[3,5,27-29] These discrepant findings may be due to the inability to adequately recreate the tumor microenvironment or because tumor vasculature is aberrant and is regulated by different physiologic signals.

A Cochrane Database analysis published in 2012[30] on ESA treatment in cancer patients showed that ESAs significantly increased mortality (HR 1.17) and worsened overall survival (HR 1.06). Importantly, an analysis restricted to trials of patients receiving chemotherapy found only an insignificant trend toward higher overall mortality (OR 1.04). It was only when the analysis was limited to trials with patients not on cancer therapy that ESA use significantly increased mortality (OR 1.23). Additional meta-analyses

TABLE 2 Guidelines for epoetin and darbepoetin in adults

Erythropoietin alfa	Darbepoetin alfa
Starting dose	
40 000U SC weekly	500 mcg Q 3 weeks
Reduce	
By 25%	By 40%
Hg increases > 1 g/dL in any 2 week period or to a level at which a transfusion can be avoided	
Increase	
To 60 000U SC weekly if Hg increases <1 g/dL after 4 weeks and remains <10 g/dL	N/A
Withhold	
Hg exceeds a level needed to avoid transfusion. Restart at 25% below the previous dose when the Hg approaches a level where transfusions may be required.	Hg exceeds a level needed to avoid transfusion. Restart at 40% below the previous dose when the Hg approaches a level where transfusions may be required.
Discontinue	
After 8 weeks if no response as measured by Hg level or If transfusions are still required.	

of controlled trials comparing patients on cancer therapy with and without ESAs have failed to show significant differences in disease progression, tumor response rates, or odds of survival between the two groups.[30-35] Several additional meta-analyses, found insufficient evidence that ESAs have any effect on progression of disease.[33,36,37]

Akin to findings in CKD patients, ESA use is associated with increased risk for thromboembolic events (TE) in cancer patients. A meta-analyses in 2013 showed that the rate of TE was higher in ESA-treated patients (RR 1.51). There were fewer TE when ESA treatment was delayed until the baseline Hb was less than 10 g/dL.[31] There is no information on what Hg targets are associated with no added mortality risk.

In composite, the results of trials on ESA use in cancer and CKD populations suggest that ESA use is associated with increased mortality and TE and that this increased risk was associated with higher Hg targets. The mortality risk with ESAs is significantly greater when patients are not receiving cancer therapy. Whether adverse outcomes are related to the total dose of ESAs or to the targeted or achieved Hg has been examined in CKD. In a meta-analysis[38] and post hoc analyses of the CHOIR[39] and TREAT[40] trials, higher ESAs doses were associated with increased risk for mortality and cardiovascular endpoints, independent of target or achieved Hg. However, these results may have been influenced by an indication bias toward higher ESA doses among patients with ESA hyporesponsiveness due to greater comorbidities and inflammation.

The complete guidelines for anemia management in CKD patients from KDIGO and in cancer patients from the ASCO and ASH can be accessed at the webpages for the respective societies.[10,11] Both guidelines propose that an initial investigation for anemia should include a history, physical exam, and diagnostic tests (CBC, reticulocyte count, serum iron, ferritin and iron saturation [TSAT], B12, and folate levels), to identify causes of anemia other than chemotherapy, a hematopoietic malignancy or CKD. The ASCO/ASH guidelines (Table 1) refer largely to solid tumors.

A review of these guidelines highlights the need for an ongoing dialog between the nephrologist and oncologist since decision making depends on patient specific factors. Implicit in the guidelines is the need for the physician to discuss the relative risks and benefits of ESAs versus RBC transfusion (tRBC) at treatment initiation and when changes in therapy occur. The ASCO/ASH guidelines specify that ESAs should be used only when the anemia in a cancer patient is the result of myelosuppressive therapy, that is, any cancer treatment, including radiation, which kills normal cells and cancer cells in the bone marrow. ESAs should only be used if the Hg is <10 g/dL and ESAs should not be used in cancer patients who are not on active treatment and for whom cancer treatment is expected to cure the disease.

For patients with symptomatic anemia, KDIGO and ASCO/ASH agree that tRBC will immediately improve symptoms, whereas ESAs can take weeks to months to provide relief. For patients with asymptomatic anemia, when deciding whether to treat with tRBCs or ESAs, the nephrologist must take into account the patient's primary cancer diagnosis, life expectancy from the cancer, risk of TE, transfusion history, comorbidities, quality of life, and risks attendant to tRBCs. The Cochrane Database analysis showed that ESA use does, as assumed, significantly decrease the risk for PRBC transfusion.[30] Of note, 1 unit of PRBC was considered significant in this analysis. One unit of RBCs may not carry any meaningful risks for viral infection or iron overload in a cancer patient with CKD who has a limited life expectancy because of one or both diagnoses. Among ESRD patients age >65 years, 30%-54.5% of patients will die within 1-year after dialysis initiation. This rate is as high as 73% for patients who are dependent on assistance for their activities of daily living.[41,42] Having an active malignancy or metastatic disease is associated with consistently worse 6-month and 1-year survival in ESRD patients.[43,44]

With the current level of donor screening, tRBC is associated with a miniscule risk of viral infections, currently 1:1 million, 1:1.2 million and 1:1.5 million for Hepatitis B, Hepatitis C and HIV, respectively.[45,46] Iron overload from tRBC is also unlikely to be a consideration in all but a few cancer patients with ESRD. Based on the approximation that each unit of RBCs has about 250 mg of iron, it's generally accepted that transfusion of 15-20 units of PRBC will result in signs of iron overload. It remains unknown if CKD patients with functional iron deficiency will manifest symptoms of iron overload with fewer units of tRBCs. Nonetheless, for patients with a relatively short life expectancy, single or repeated tRBC generally will not engender clinically significant sequelae. For those who have bone marrow failure, are ESA unresponsive, and who become iron overloaded is due to transfusion dependence, chelation therapy may be required.

Practical considerations will also influence the decision regarding the use of ESAs or tRBC. Since most outpatient dialysis units will not perform tRBC, this prescription requires a visit to another treatment facility as well as additional venipuncture, both of which can be difficult in ESRD patients. The presence of volume overload, history of transfusion reactions, and religious objections to blood products would argue against tRBC. Insurance coverage for ESA therapy may be an issue for some patients.

Despite data indicating that ESA use in patients on chemotherapy does not increase mortality risk or progression of disease, and the absence of any study or meta-analyses of ESA treatment outcomes by subgroups based on treatment intent, ASCO/ASH recommends that ESA not be offered to patients whose cancer treatment is intended to cure. KDIGO recommends "caution" when cure is anticipated. Advances in precision medicine and biologic therapies have bolstered disease-free intervals and progression free survival, making clinical outcomes from cancers a moving target such that the distinction between treatment aimed at "palliation" or "cure" is not always categorical. For example, the FDA recently granted approval for two CAR T-cell therapies[47,48] based on clinical trials that demonstrated overall response and complete remission rates of 80% and 60%, respectively, in patients who previously had resistant and multiply relapsed hematologic malignancies prior to the biologic therapy.

For a patient whose cancer is potentially curable and who may become a candidate for a renal transplant in the future, the hazards associated with allosensitization would seem to favor ESAs. Two database analyses of matched cohorts of patients awaiting primary renal transplant revealed that, when compared to nontransfused patients, transfused patients have clinically significant increases in HLA antibody levels and panel reactive antibody.[49,50] Currently, it remains unclear if leukoreduction reduces the incidence of allosensitization from tRBC.[51,52] Thus the choice of tRBC over ESA may reduce the likelihood of transplantation. In general, 2 years is the minimum disease-free time interval after treatment of a cancer for a patient to become eligible for a renal transplant. Exceptions to this time criteria include breast cancer beyond in situ lesions, malignant melanoma, node positive colorectal cancer, and invasive cervical cancer, for which some societies recommend a 5-year interval.[53,54] Patients who are healthy enough to be listed for a renal transplant after being cured of their cancer may still have a significant wait on a transplant list if they do not have a live donor. Thus, for cancer patients who have a reasonable expectation to become a viable renal transplant candidate in the future, minimizing the risk of both allosensitization associated with tRBC as well as any potential protumorigenic role for ESAs are appropriate.

ASCO/ASH do not provide a nadir Hg value at which ESAs can be started. For ESRD patients, KDIGO recommends avoiding Hg levels below 9g/dL, presumably because cardiovascular disease is highly prevalent among ESRD patients. It's been my experience that younger patients and those without significant cardiovascular disease or numerous comorbidities can reasonably tolerate Hg values as low as 7-7.5 g/dL. For older patients or those with significant cardiovascular disease and additional comorbidities, it may be reasonable to consider initiation of ESAs between 8 and 8.5 mg/dL or at a threshold value where the patient is known to become symptomatic.

As previously stated, meta-analyses demonstrate an approximately 50% increase risk of TE in patients with cancer receiving ESAs with fewer TE when ESA treatment was delayed until the baseline Hb was <10 g/dL. The absolute pooled event rate in the treatment and control arms were 5.8% and 3.2%, respectively, with ranges of 0%-30.8% and 0%-14.5%, respectively.[31] Notably, specific risk factors for TE were not identified in these analyses and there was no threshold level below which no risk was evident. Based on these findings, ASCO/ASH guidelines nebulously recommend exercising caution when ESAs are used concomitantly with treatment strategies and diseases where the risk of TE is increased and that the clinician must weigh the risks of TE and benefits of ESA in an individual patient. Additionally, ESA therapy can be considered when the Hg is <10 g/dL but should probably not be used until substantially below this level and then only at lowest dose to minimize symptomatic anemia and tRBC.

Epidemiological studies show that tumors of the pancreas, brain, lung, and ovary are associated with the highest risk of TE.[41,55] Relatively low risks are observed with breast and prostate cancer.[55] Surgery and hormonal therapy are both associated with increased risk of TE in cancer patients. Of note these treatments are often used for the management of breast and prostate cancer. Antiangiogenic drugs are also associated with an increased risk for TE.[55] In general, cancer types that are biologically aggressive as manifested by short survival time and early metastatic spread are correlated with a higher incidence of thrombosis.[56] Across a range of cancer types, metastatic disease at the time of cancer diagnosis was found to be the strongest predictor of subsequent venous thrombosis.[57] In general, the incidence of TE is highest within the first 3 months of cancer diagnosis and remains elevated but relatively decreased between 3-12 months. The lower risk observed beyond 1 year may be due to response to cancer treatment or to patients succumbing to their disease.[58]

Based on these data, it may be prudent to avoid ESAs in patients with a newly diagnosed malignancy, a history of TE, metastatic disease at presentation, tumors with aggressive features, or with any treatment that includes surgery, hormonal or antiangiogenic therapy. Overall, the risk for TE is greater among inpatients, but the majority of TE occur in outpatients (about 80%) because most patients are treated in outpatient settings.[59] The ASCO/ASH guidelines on ESA use do not include a discussion on thromboprophylaxis. Those recommendations were made in a separate document[60] in which ASCO/ASH recommends initiating pharmacologic thromboprophylaxis with oral anticoagulants or low molecular weight heparin prior to starting systemic chemotherapy in patients at high risk for TE, unless there is a clinical contraindication. To determine risk, ASCO recommends using the Khorana[61] score and to begin thromboprophylaxis for patients on systemic chemotherapy who have a score of 2 or higher. A Hg below 10g/dL and ESA use each alone confer

a score of 1. Tumors of the pancreas and stomach have a score of 2 and gynecologic, genitourinary (except prostate), and lung cancers have score of 1.

ASCO/ASH makes one exception to its recommendation that ESAs be used only for patients who are on palliative cancer therapy. It has been demonstrated that patients with myelodysplastic syndrome (MDS) and a serum EPO level ≤500 IU/L had marked increases in Hg levels with ESAs.[62] Nephrologists do not routinely check serum EPO levels in CKD patients but ASCO/ASH suggests that EPO levels be checked in patients with lower risk MDS. For patients with other hematologic malignancies like myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia who are receiving concurrent myelosuppressive therapy, it is recommended that the clinician evaluate the hematologic response to cancer treatment before considering ESA use.

If the decision is made to begin ESAs, it is recommended that the clinician follow the FDA dosing guidelines (Table 2). With respect to efficacy and safety, EPO beta and alpha, darbepoetin, and biosimilar epoetin alfa are considered equivalent. A meta-analysis showed that up to 46% of patients with no rise in Hg by 2-4 weeks will ultimately respond to ESAs.[63] However, if a patient's Hg does not increase 1-2 g/dL, or their need for blood transfusions is not decreased after 6-8 weeks on ESAs, this is considered an ESA treatment failure and the ESA should be discontinued. At that time, such patients should be reevaluated for causes of ESA resistance like tumor progression, blood loss, marrow replacement by disease or marrow suppression from medications, and infection.

Clearly there are numerous gaps in our knowledge of anemia management in patients with CKD and a prior or present cancer diagnosis. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHI) are a novel class of orally available molecules and represent a new therapeutic strategy for anemia in CKD. This innovation will likely import even greater uncertainty for anemia management for CKD patients with cancer. Currently, there are 5 HIF-PHI products being investigated in human subjects with nondialysis-dependent and dialysis-dependent CKD. Targeting the HIF pathway with HIF-PHIs may help to circumvent functional iron deficiency as a result of elevated hepcidin levels. In clinical trials, HIF-PHIs induce erythropoiesis in the presence of normal oxygen tension, decrease hepcidin levels and consequently increase the bioavailability of iron.[64]

The HIF protein was found 1991 next to the EPO gene during the early studies on ESAs. In response to hypoxia, HIF-1α expression is up-regulated and the molecule translocates from the cytoplasm to the cell nucleus where it forms a functional heterodimer with the HIF-β subunit. This complex acts as a transcriptional factor for hundreds of genes involved in angiogenesis, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and angiopoietin-1 (ANGPT1).[65] In addition to regulating the expression of genes involved with tumor growth, invasion, and metastasis,[66] the HIF pathway plays a key role in the development of resistance to anti-cancer therapies[67] and HIF-1α facilitates escape of tumor cells from T-cell recognition.[68]

Increased HIF expression in a range of human cancers is associated with poorer prognosis and outcomes.[69] It remians unclear if HIF is acting as a tumor promoter or if higher HIF levels just reflect a more hypoxic milieu in faster growing and more aggressive tumors. While there is a theoretical concern that HIF-PHIs may be protumorigenic, there are no clinical data that demonstrate causality. In fact, everolimus and temsirolimus, which are both indirect HIF inhibitors in the class of mTOR inhibitors, are effective against several tumor types, including renal cell carcinoma. There are several ongoing Phase II and III clinical trials of HIF inhibitors across several tumor types[65] which may help to better clarify the complicated interplay between HIF inhibitors and tumorigenesis.

In summary, the guidelines for anemia management in patients with cancer and CKD are not based on high-quality experimental or clinical data that verifiably demonstrate a causal relationship between ESAs, CKD, cancer, and TE. ASCO/ASH states that ESAs should only be used to treat anemia that is the result of myelosuppressive therapy in cancer patients. This narrowly defined indication for ESA use in cancer patients is not meaningful for clinicians caring for patients with CKD and cancer who are on myelosuppressive therapy since it is impossible to determine the exact etiology of anemia in such patients. The diagnostic value of serum EPO levels in patients with advanced CKD is of limited benefit.[70] Moreover, the results of several meta-analyses suggest no increased risk for cancer-related complications if patients are receiving ESAs on cancer therapy.

For patients with symptomatic anemia, tRBCs seems to be the most prudent intervention. For patients with asymptomatic anemia. a more tactical approach may provide greater benefit and minimize harm. It may be best to avoid tRBC for patients who may require a renal transplant in the future if you think that the patient will survive with no evidence of disease for long enough to qualify for a transplant. For patients at high risk for TE (recent surgery, immobility, or who are receiving anti angiogenic or hormonal therapy), it may be reasonable to begin thromboprophylaxis with an oral anticoagulant or low molecular weight heparin prior to starting cancer therapy and then consider ESA use after there has been some response to treatment. For patients with a poor functional status, significant comorbidities, and whose cancer prognosis is poor, tRBCs and ESA may both be reasonable approaches to anemia management depending on patient preference and comfort. ESAs should probably be started at a Hg level at which the patient has not developed symptoms related to anemia but below which the clinician anticipates that the patient will become symptomatic. For younger patients without significant comorbidities, this may be as low as 7.5 g/dL. For older patients and those with cardiovascular disease, 8-8.5 g/dL may be a reasonable threshold.

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