ACKD Advances in Chronic Kidney Disease

A Journal of the National Kidney Foundation®

Vol 26, No 4, July 2019

EDITORIAL

Erythropoiesis-Stimulating Agents and Cancer: Myth or Truth

Erythropoiesis-stimulating agents (ESAs) have been implicated in causing cancer progression. This belief has been largely based on trials in the early 2000s of ESA use in malignancy with high hemoglobin (Hgb) targets and large ESA doses to attain the targets. More recent trials using ESA doses with Hgb targets similar to current goal levels in CKD have not confirmed this increased risk of cancer progression for most malignancies.

Anemia in patients with malignancy was associated with increased mortality and decreased response to therapy. Correction of anemia was postulated to enhance survival rates[1,2] by increasing tumor oxygenation, which would lead to greater susceptibility to chemotherapy and radiotherapy.[3-7] However, the outcomes of three early trials using ESAs were abysmal. The double-blinded, placebo-controlled trial of erythropoietin (EPO) to treat head and neck cancer patients with anemia undergoing radiotherapy ($n = 351$) examined response to radiotherapy when anemic patients (Hgb: <12 g/dL for women and <13 g/dL for men) were corrected to higher target levels (>14 g/dL in women and >15 g/dL in men).[3] The ESA group had increased cancer progression (relative risk [RR], 1.69; $P = 0.007$) and death (RR, 1.39; $P = 0.02$). The Danish Head and Neck Cancer (DAHANCA) 10 trial randomized 522 patients with or without darbepoetin alfa (DA) to a target Hgb of 14.0–15.5 g/dL.[4] The placebo group had a 10% improved survival rate ($P = 0.01$) compared with the ESA-treated group, prompting trial termination. The multicenter, randomized, double-blinded, placebo-controlled Breast Cancer Erythropoietin Trial (BEST) of women with metastatic breast cancer receiving first-line chemotherapy examined survival difference in those with EPO treatment for anemia vs placebo.[8] Hgb was targeted to 12–14 g/dL in subjects with baseline levels of 13 g/dL. The study was also terminated early as the primary endpoint of 12-month survival in the ESA-treated group was worse than the placebo group (70% vs 76%). This was attributed to cancer progression and increased thrombotic and vascular events in the ESA group.

A Cochrane Database meta-analysis of 91 trials also documented greater mortality risk in ESA-treated participants with malignancy, defined as death occurring up to 30 days after active study protocol (hazard ratio [HR], 1.170; 95% confidence interval [CI], 1.06 to 1.29), with reduced overall survival (HR, 1.05; 95% CI, 1.00 to 1.11).[9] These results were restricted to those with baseline Hgb levels >12 g/dL—a level that currently prohibits the initiation of ESA therapy. In trials restricted to active chemotherapy, only modest trends toward on-study (odds ratio [OR], 1.10; 95% CI, 0.98 to 1.24) and overall mortality (OR, 1.04; 95% CI, 0.98 to 1.11) were recorded. ESA use was associated with thromboembolic complications (RR, 1.52; 95% CI, 1.34 to 1.74) at any baseline Hgb.

In these trials, ESA doses were substantial (EPO β dose of 300 IU/kg subcutaneously 3 times weekly,[3] DA 150 mcg subcutaneously weekly,[4] and EPO 40,000 U subcutaneously once weekly[8]) with high Hgb targets. Consistent with the aforementioned trials, the Cochrane database meta-analysis reported on trials with target Hgb levels considerably higher than present targets with an upper Hgb level <14 g/dL in 54% of studies, <15 g/dL in 24%, and <16 g/dL in 5%. The reasons for higher mortality with ESA use in these early studies may have been attributable to enhanced thrombotic rates, given the considerable ESA doses required to achieve high Hgb targets. This observation represents an adjunctive and/or alternative explanation to the possibility of cancer progression.[5]

In contrast to the findings of earlier trials, ESAs have not been shown to increase tumor progression in the majority of more recent human studies.[9] Prior versions of the Cochrane meta-analysis included dosages of at least 300 U/kg body weight per week (epoetin alfa and beta) delivered for at least 4 weeks. This criterion was removed to include studies or study arms with lower dosages. A meta-analysis of ESA use and safety outcomes, which included

1548-5595/$36.00
https://doi.org/10.1053/j.ackd.2019.04.001

25 studies with some measure of disease progression,[10] found no significant impact on cancer progression (OR, 1.01; 95% CI, 0.9 to 1.14). A summary of meta-analyses of 56 trials and 16,336 participants also did not demonstrate any ESA effect(s) on disease advancement.[11]

A recent trial of 2098 women with metastatic breast cancer could not rule out a 15% increased risk of progressive disease or death with EPO alfa use vs best standard of care when Hgb was <11 g/dL with target Hgb concentration <12 g/dL.[12] Although the median progression-free survival (HR, 1.089; 95% CI, 0.99 to 1.20) and median overall survival (HR, 1.057; 95% CI, 0.95 to 1.18) exceeded the predefined noninferiority margin of 1.15, which was the upper boundary of the 95% CI, the independent review committee concluded that progression-free survival did meet noninferiority criteria.

Based on data reporting increased mortality and thrombotic risk, the American Society of Clinical Oncology/American Society of Hematology and the European Society for Medical Oncology in 2010 developed guidelines for ESA use in patients with cancer. Advice was to start ESA therapy in case of chemotherapy-induced anemia for Hgb < 10 g/dL and to discontinue ESA therapy within one month of chemotherapy completion.[13,14] The guidelines removed an optimal target Hgb level and recommended prescribing the lowest possible therapeutic ESA dose. For myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia patients, the American Society of Clinical Oncology/American Society of Hematology authored two specific recommendations. First, observe Hgb responses to chemotherapy. Second, manage symptoms using red cell transfusions, with the known risk of thromboembolic disease documented in myeloma patients treated with thalidomide, lenalidomide, doxorubicin, or corticosteroids.[13,15]

Inferior outcomes associated with ESA use in malignancy were postulated as attributable activation of erythropoietin receptors (EpoRs) on tumor cells. Receptor-ligand engagement presumably would enhance the proliferation of tumor cells.[16,17] Early studies revealed expression of EpoR mRNA and protein by immunoblotting on tumor cells. However, these findings have been questioned due to the absence of negative controls and lack of assessment of functional responses to Epo. These findings may be due to the use of nonspecific EpoR antibodies that identify multiple non–EpoR proteins. In addition, these antibodies detect cytoplasmic EpoRs instead of functional membrane-associated EpoRs.[18-20] Other studies have not shown significant gene amplification of tumoral EpoR[20] when using EpoR-specific monoclonal antibodies. These antibodies detected EpoR levels that were either undetectable or 100-fold lower in tumor cell lines than EpoR levels in positive-control hematopoietic cell lines.[21] Disagreement regarding the presence or absence of EpoR on tumor cells stems from the antibody used for detection. Academic scientists have usually used polyclonal anti-EpoR antisera, whereas scientists working for industry have used monoclonal antibodies.[21] The absence or rare functional responses to *in vivo* ESA administration in tumor cell lines implies that tumor cell EpoR activation does not represent a major mechanism for cancer spread.

Other mechanisms for ESA use leading to tumor progression include binding of EpoRs on activated monocytes and macrophages, repression of proinflammatory genes with subsequent immunosuppression and tumor enhancement, and triggering of pathways that increase tissue delivery of oxygen to tumor. The latter potentially leads to lymphangiogenesis with lymph node metastasis with resultant tumoral progression.[11,21-24]

Oncology guidelines do not address specific treatment of cancer patients with anemia in CKD. In 2009, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) compared DA treatment vs placebo randomizing diabetic CKD patients with estimated glomerular filtration rate levels from 20 to 60 mL/min per 1.73 m^2 and anemia with Hgb ≤11 g/dL to a target of 13 g/dL.[25] The DA therapy group did not have reduced risk of the composite outcomes (death, cardiovascular event and death, or ESRD) but had an increased incidence of fatal and nonfatal strokes (HR, 1.92; 95% CI, 1.38 to 2.68; $P < 0.001$). Uneasiness regarding greater mortality among patients with cancer during the study led to changes in protocol to exclude individuals with active cancer and discontinue DA in any patients who developed cancer. No difference occurred in the number of cancer-related events or deaths in the ESA-treated group; however, more cancer-related deaths occurred in the ESA subgroup with a history of cancer that preceded randomization by at least 5 years (ESA, 14 deaths vs placebo, 1 death; $P = 0.002$). These findings implied that a previous history of malignancy in combination with ESA use (which in this trial targeted an Hgb level of 13 g/dL) may be harmful in this diabetic CKD population.

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for anemia in CKD recommended caution with initiation or maintenance of ESA therapy in those with previous malignancy only after assessment of the potential benefits of reduction of anemia symptoms and transfusion requirements vs the risk of stroke, vascular access clotting, and hypertension for all patients with CKD.[26] ESAs were specifically recommended for use with great caution, if at all, in CKD patients with active malignancy, particularly when cure was anticipated (grade 1B) and with a previous malignancy (grade 1C).

Information apropos the association of ESAs and incidence of novel cancers is limited. In the Surveillance of Epoetin-Adverse Events of Stroke and Cancer (SEASCAN) cross-sectional study, 7415 individuals with CKD of stages 4 or 5 received either 0, <6 months, or ≥6 months of EPO treatment.[27] No significant differences in incident cancer diagnosis among EPO groups were established (2.4%, 3.4%, and 2.5% for 0, <6-month, and ≥6-month groups; $P = 0.836$). Mean baseline Hgb levels were 10.3 and 10.0 in the <6-month and ≥6-month groups, respectively. The length of follow-up appeared relatively short, thereby limiting conclusions.

A nested case-control study of 4574 patients on dialysis evaluated ESA dose exposure 6–9 months before cancer

diagnosis.[28] Exposure categories were unexposed, low-dose DA (<30 mcg/week), moderate-dose DA (30–70 mcg/week), and high-dose DA (>70 mcg/week) with baseline Hgb levels of 10.6 g/dL in untreated and ESA-treated groups. Epoetin alfa doses were converted to DA doses using a ratio of 200 EPO units to 1 mcg of DA. With a median follow-up of 1.8 years (interquartile range, 0.9–3.1), DA exposure was associated with a higher risk of cancer (OR, 1.04; 95% CI, 1.02 to 1.07). This increased risk was observed in the high-dose group (OR, 1.77; 95% CI, 1.18 to 2.66), which was not encountered among the other dose groups compared to the unexposed group. Subjects with high-dose ESA exposure may have incurred an inflammatory process or experienced a "missed" prior malignancy to explain the increased cancer risk in addition to or instead of the ESA-induced or ESA-accelerated cancer growth.

In summary, data are insufficient to support an association of low-dose ESA administration with increased cancer risk. Although one trial could not rule out increased risk of progression with a Hgb target <12 g/dL, most studies show that cancer patients with CKD had an increased mortality risk with ESA only when baseline Hgb concentrations exceeded 12 g/dL and targets were 13–16 g/dL.[10,27] The paucity of data supporting tumor progression in most malignancies may result from an ESA effect limited to specific tumor types such as head, neck, and breast cancers. Alternatively, the contribution of elevated target Hgb level, high ESA dose, lack of anemia before starting therapy, or a combination of these factors to the poor outcomes associated with early studies of ESA therapy is unclear. There are worse outcomes independent of cancer progression with high Hgb targets, such as stroke and thromboembolic risk, with the latter risk being increased further with malignancy.

CKD patients with active malignancy may have anemia due to chemotherapy, radiation treatment, inflammation, and multiple venipunctures, in addition to the anemia of Epo deficiency, iron deficiency, and inflammation from CKD. KDIGO anemia guidelines cautiously recommend ESA initiation with previous or active malignancy, whereas the United States Food and Drug Administration recommends the following: ESA use only during chemotherapy when anemia is ascribed to chemotherapy and no ESA administration if chemotherapy is considered curative. However, cancer patients with CKD or ESRD will have continued ESA requirements beyond the period of chemotherapy and cure of cancer. Transfusions in patients with CKD/ESRD may be problematic due to vascular access, volume overload with transfusions on nondialysis days, or an inability to provide transfusions during dialysis. ESA symptom management from the anemia in CKD and transfusion reduction may be more beneficial to an individual than the small potential for incident cancer risk.

Michael J. Choi, MD
Division of Nephrology and Hypertension
MedStar Georgetown University Hospital
Washington, DC

Jerry Yee, MD
Editor-in-Chief
Henry Ford Hospital
Detroit, MI
Professor of Clinical Medicine
Wayne State University
Detroit, MI

Support: None.
Financial Disclosure: No relevant disclosures for either author.

REFERENCES

1. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival of patients with cancer: a systematic, quantitative review. *Cancer.* 2001;91(12):2214-2221.
2. Glaspy J, Dunst J. Can erythropoietin therapy improve survival? *Oncology.* 2004;67(Suppl 1):5-11.
3. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double blind, placebo controlled trial. *Lancet.* 2003;362(9392):1255-1260.
4. Overgaard J, Hoff CM, Hansen HS, et al. DAHANCA 10 - Effect of darbepoetin alfa and radiotherapy in the treatment of squamous cell carcinoma of the head and neck. A multicenter, open-label, randomized, phase 3 trial by the Danish head and neck cancer group. *Radiother Oncol.* 2018;127(1):12-19.
5. Hazzan AD, Shah HH, Hong S, Sakhiya V, Wanchoo R, Fishbane S. Treatment with erythropoiesis stimulating agents in chronic kidney disease patient with cancer. *Kidney Int.* 2014;86(1):34-39.
6. Semenza GL. Hypoxia, Clonal Selection, and the role of HIF–1 in tumor progression. *Crit Rev Biochem Mol Biol.* 2000;35(2):71-103.
7. Van Belle SJ, Cocquyt V. Impact of hemoglobin levels on the outcomes of cancers treated with chemotherapy. *Crit Rev Oncol Hematol.* 2003;47(1):1-11.
8. Leyland–Jones B: on behalf of the BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol.* 2003;4:459-460.
9. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev.* 2012;(12):CD003407.
10. Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis–stimulating agents in oncology: a study–level meta–analysis of survival and other safety outcomes. *Br J Cancer.* 2010;102(2):301-315.
11. 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(7):1249-1258.
12. Leyland–Jones B, Bondarenko I, Nemsadze G, et al. A randomized, open–label, multicenter, phase III study of epoetin alfa versus best standard of care in anemic patients with metastatic breast cancer receiving standard chemotherapy. *J Clin Oncol.* 2016;34(11):1197-1207.
13. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Somerfield MR, Temin S. American Society of Clinical oncology/American Society of Hematology Clinical Practice guidelines update on the use of epoetin and darbepoetin in adult patients with cancer. *J Oncol Pract.* 2010;6(6):317-320.
14. Schrijvers D, Desamblant H, Rolla F: ESMO Guidelines Working Group. Erythropoiesis–stimulating agents in the treatment of anemia in cancer patients: ESMO Clinical Practice Guidelines for use. *Ann Oncol.* 2010;21(Suppl 5):v244-v247.
15. Bennett CL, Angelotta C, Yarnold PR, et al. Thalidomide–and lenalidomide–associated thromboembolism among patients with cancer. *JAMA.* 2006;296(21):2555-2560.
16. Acs G, Acs P, Beckwith SM, et al. Erythropoietin and erythropoietin receptor expression in human cancer. *Cancer Res.* 2001;61(9):3561-3565.

17. Hencke M, Mattern D, Pepe M, et al. Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol.* 2006;24(29):4708-4713.
18. Laugsch M, Metzen E, Svensson T, Depping R, Jelkmann W. Lack of functional erythropoietin receptors of cancer cell lines. *Int J Cancer.* 2008;122(5):1005-1011.
19. Sinclair AM, Rogers N, Busse L, et al. Erythropoietin receptor transcription in neither elevated nor predictive of surface expression in human tumour cells. *Br J Cancer.* 2008;98(6):1059-1067.
20. Swift S, Ellison AR, Kassner P, et al. Absence of functional EpoR expression in human tumor cell lines. *Blood.* 2010;115(21):4254-4263.
21. Bennett CL, Lai SY, Sartor O, et al. Consensus on the Existence of functional erythropoietin receptors on cancer cells. *JAMA Oncol.* 2016;2(1):134-136.
22. Nairz M, Schroll A, Moschen AR, et al. Erythropoietin contrastingly affects bacterial infection and experimental colitis by inhibiting nuclear factor–κB–inducible immune pathways. *Immunity.* 2011;34(1):61-74.
23. Lee AS, Kim DH, Lee JE, et al. Erythropoietin induces lymph node lymphangiogenesis and lymph node tumor metastasis. *Cancer Res.* 2011;71(13):4506-4517.
24. McKinney M, Arcasoy MO. Erythropoietin for oncology supportive care. *Exp Cell Res.* 2011;317(9):1246-1254.
25. Pfeffer MA, Burdmann EA, Chen CY, et al: for the TREAT Investigators. A trial of darbepoetin alfa in type 2 Diabetes and chronic kidney disease. *N Engl J Med.* 2009;361(21):2019-2032.
26. KDIGO Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int.* 2012;2(4):280-335.
27. Imai E, Yammato R, Suzuki H, Watanabe T. Incidence of symptomatic stroke and cancer in chronic kidney disease patients treated with epoetins. *Clin Exp Nephrol.* 2010;14(5):445-452.
28. Rene E, Lazrak HH, Laurin LP, Elftouh N, Vallee M, Lafrance JP. Association of the erythropoiesis –stimulating agents and the incidence risk of cancer diagnosis among chronic dialysis patients: a nested case–control study. *Nephrol Dial Transplant.* 2017;32(6):1047-1052.