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Intersecting Guidelines: Administering Erythropoiesis-Stimulating Agents to Chronic Kidney Disease Patients with Cancer

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Abstract

There has been a dramatic sea change in the use of erythropoiesis-stimulating agents (ESAs) for anemic persons with chronic kidney disease (CKD) or cancer patients undergoing chemotherapy. An important area that has not been addressed previously is a CKD patient who also has a malignancy. Clinical guidelines exist that outline recommended treatments for each disease, but the intersection of the two disease processes presents difficult decisions for patients and physicians. Herein, we review the background underlying recent revisions in clinical alerts and guidelines for ESAs, and provide guidance for treating anemia among CKD patients who are receiving no therapy, chemotherapy with curative intent, or chemotherapy with palliative intent. The guiding principle is that comprehensive assessment of risks and benefits in the relevant clinical setting is imperative.

The past year has been marked by a dizzying array of safety notifications for administration of erythropoiesis-stimulating agents (ESAs) to persons with chronic kidney disease (CKD) as well as to persons with cancer. However, administration of ESAs to persons with both CKD and cancer is an area that has not been addressed, although almost one-third of end-stage renal disease (ESRD) patients also have a cancer diagnosis (1). This observation raises compelling arguments to reassess the potential benefits and risks of ESA treatment for these individuals. Since 2006, the Food and Drug Administration, ESA manufacturers, the National Kidney Foundation, the American Society of Clinical Oncology, the American Society of Hematology, and the National Comprehensive Cancer Network have issued a series of clinical alerts redefining the risks and benefits of ESA treatment for persons with

cancer or ESRD. In fact, the first such alert, disseminated in March 2007, was directed at both cancer and CKD populations (2).

Erythropoiesis-stimulating agent manufacturers have revised package inserts for CKD and cancer patients, recommending that physicians use the lowest doses of ESAs that would prevent patients with either diagnosis from receiving red blood cell transfusions. Subsequent advisories have disseminated messages separately to clinicians who provide care for CKD patients and clinicians who provide care for cancer patients. What should clinicians do when faced with a patient who has both CKD and cancer—which advisory is more appropriate to follow? In an effort to provide guidance to clinicians, assessment of the current views of risks and benefits for ESA administration in the CKD and the oncology setting is needed.

ESA Administration for CKD Patients

Basic science and animal studies provide evidence of putative clinical benefits when ESAs are administered to CKD patients. Erythropoietin receptors (EpoR), EpoR messenger RNA, and EpoR signaling in the heart, central nervous system, blood vessels, kidneys, testes, and the female reproductive tract and erythropoietin-associated neurotrophic and neuroprotective effects have been reported (3). Animal experiments identified erythropoietin (Epo) protection from ischemia-reperfusion injury (4), promotion of ventricular remodeling after coronary ligation (5), and protection against hypoxia-induced apoptosis (6). However, clinically, the benefits of ESA administration to CKD patients have been observed primarily with respect to avoidance of blood transfusions.

Clinical trials, including hemodialysis and nonhemodialysis CKD patients, have been designed to show improvements in cardiac function with ESA treatment of anemia, yet have failed to identify improved cardiac outcomes or improved survival rates when ESAs were administered with hemoglobin levels targeted for complete anemia correction versus partial anemia correction (7). In fact, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study found poorer composite outcomes (adverse cardiac outcomes and mortality) when CKD patients receiving hemodialysis were administered ESAs targeted to higher versus lower hemoglobin levels (8). Additional review of clinical trial data revealed poorer outcomes when CKD patients received high ESA doses, independent of whether the target hemoglobin level represented partial or full correction of anemia. Additionally, increased risks of arterial thrombotic events (myocardial infarction, cerebrovascular accidents, and thrombosis of the access site) were identified when high doses of ESAs were administered (9).

These findings resulted in the most recent recommendations by the Food and Drug Administration's (FDA) Cardio-renal and Drug Safety Advisory Boards in September 2007. The advisory board recommended avoiding hemoglobin levels greater than 13 g/dL, targeting hemoglobin levels between 10 and 12 g/dL for patients receiving hemodialysis, and restricting large ESA doses in CKD patients who show no significant rise in hemoglobin (termed hyporesponders) (10). The benefits of ESA administration were identified as preventing transfusions (thereby minimizing iron overload and potential alloimmunization); statements outlining potential health-related quality of life benefits were removed from the FDA-approved package insert. Consistent with associated risks and benefits, the Kidney Disease Outcomes Quality Initiative now recommends targeting hemoglobin levels between 11 and 12 g/dL, avoiding hemoglobin levels of > 13 g/dL, and avoiding administration of high doses of ESAs to persons with CKD.

ESA Administration for Cancer Patients

Basic science of cell lines and tumor samples from one randomized clinical trial and clinical findings from 8 randomized clinical trials provide evidence of adverse effects on tumor cells and/or patient survival when patients with solid cancers receive ESAs. In 2001, Acs et al. identified basal and hypoxia-stimulated expression of erythropoietin and its receptor EpoR in human breast cancer cells, but not with normal breast, benign papilloma, or fibrocystic tissue (11).

In 2003, Henke et al. (12) and Leyland-Jones (13) reported poorer survival rates when cancer patients with head and neck cancer undergoing radiation therapy or women with breast cancer undergoing chemotherapy received ESAs versus placebo, respectively. In October 2006, Henke et al. reported that head and neck cancer patients who had participated in the aforementioned 2003 randomized trial demonstrated decreased locoregional progression-free survival if epoetin beta had been administered to patients whose tumors demonstrated EpoR expression (14). At the 2008 ASCO conference, Blau et al. reported that ESA-treated head and neck cancer patients included in the Henke et al. 2003 trial who had unresected tumors and higher than median levels of EpoR mRNA expression had poorer loco-regional tumor control than patients who received placebo (15,16).

Eight recently reported phase III trials have identified poorer outcomes (mortality and/or tumor progression rates) when cancer patients with treatment-associated anemia received ESAs versus placebo/control (17). One additional phase III trial identified poorer survival rates when cancer patients who were not receiving active therapy received ESAs versus placebo (18). Moreover, a comprehensive meta-analysis of 51 phase III trials reported in February 2008 identified poorer survival rates when cancer patients received ESAs versus placebo.

Taken together, these findings raise concern that ESA administration might stimulate tumor cell growth in cancer patients. Advisories from the FDA's Oncologic Drug Advisory Committee in May 2007 and again in March 2008, the National Comprehensive Cancer Network in February 2008, and the European Medicines Agency in June 2008, advise clinicians to avoid administering ESAs to anemic cancer patients who are not receiving active therapy or who have curable malignancies (19–22). Most recently, in July 2008, the FDA requested that the manufacturers' revised package inserts state that ESAs are not indicated for the treatment of chemotherapy-related anemia among cancer patients who are receiving therapy with curative intent (23,24). For patients with chemotherapy-associated anemia who are being treated without curative intent, target hemoglobin levels of less than 10 g/dL have been established by the Centers for Medicare and Medicaid Studies (for reimbursement purposes), while the FDA requested that ESA manufacturers remove all text from package inserts for ESA treatment of chemotherapy-related anemia related to trigger and target hemoglobin levels (23–25). An additional concern is that meta-analyses have found that cancer patients have significantly increased risk of venous thromboembolism (VTE) when exposed to ESAs versus placebo/control.

Synthesizing the CKD and Cancer Advisories

While no formal guidelines provide recommendations for use of ESAs among CKD patients with cancer, the above material provides important insights for this difficult clinical scenario. The overlap of the CKD and the cancer advisories leads one to consider varying recommendations for CKD patients with cancer, depending on malignancy type and current treatment.

If a CKD patient has a solid tumor and is not undergoing active therapy (where evidence of ESA-induced tumor progression appears to be strongest), then patients should be informed that one large randomized trial found poorer outcome among cancer patients who received ESAs and were not receiving active therapy. Anemic CKD patients in this setting would be wise to consider treatment of their severe anemia with blood transfusions to minimize risk of tumor stimulation by avoiding ESAs.

If a CKD patient has a solid tumor and is receiving curative or adjuvant chemotherapy, then patients should be informed of the potential risks of ESA stimulation of tumor cells when these chemotherapy treatments are being administered. For CKD patients with breast or head and neck cancer and who have curable malignancies and are receiving chemotherapy, clinicians and patients may consider red blood cell transfusions as needed to prevent development of clinically symptomatic anemia during the period of time that the patient is receiving chemotherapy. When the period of active chemotherapy is completed, ESA treatment should be administered with caution and in concordance with current guidelines, as cancer patients may have microscopic residual tumors.

If a CKD patient has a solid tumor and is receiving palliative chemotherapy, then the patient should be informed that the potential benefits of ESAs are to prevent transfusions (for both the cancer and CKD indication). Additionally, risks of ESA administration include stimulation of tumor cells, arterial thrombosis, and VTE. Moreover, some new drugs, especially antiangiogenic compounds combined with chemotherapy, pose an additional risk of thromboembolism, and thus should not be combined with ESAs (26). Overall, for these patients whose hemoglobin levels are in the range where treatment is indicated (based on clinical findings and/or hemoglobin levels < 10 g/dL), risk–benefit assessment would tend to favor administering ESAs rather than blood transfusions. However, additional considerations such as history of malignancy-associated hypercoagulable state, prior thrombosis, or current drug regimen may alter the risk–benefit ratio.

If a CKD patient has a hematologic malignancy and is receiving chemotherapy, then patients should be informed of the potential for ESA-associated VTE; however, no trials have reported evidence of ESA inducing tumor progression or even ESA-associated increases in death rates in these settings. If the patient is aware of the associated risks and prefers to receive ESAs over transfusions, then ESAs should be considered preferentially. However, if the patient prefers to receive transfusions because of concerns of ESA-associated risks of VTE or pulmonary embolism, then transfusions should be considered preferentially. For example, a multiple myeloma patient with CKD who is receiving thalidomide or lenalidomide with dexamethasone would likely be at very high risk of developing VTE complications when concomitantly receiving ESAs. However, prophylaxis for VTE with low molecular weight heparin or possibly aspirin may decrease VTE risks while chemotherapy and ESAs are being administered (27).

Summary

Concurrent CKD and cancer is important to consider when devising treatment strategies for these unfortunate individuals who live at the intersection of these two diseases. Risks of mortality and tumor progression when ESAs are administered alongside chemotherapy to cancer patients with solid cancers appear to be related to the off-target effects of the ESAs rather than the target or achieved hemoglobin level. In contrast, for CKD patients, ESA toxicity appears to be related to the target hemoglobin level and/or administration of high ESA doses. At the intersection of CKD and cancer, the prudent physician must personalize the use of ESAs. Overall, if risks outweigh the benefits, such as may be the case for a CKD patient with a curable cancer receiving chemotherapy, the goal should be to avoid ESAs

entirely. If ESA-associated risks are less apparent, as may exist for patients with hematologic malignancies or noncurable solid cancers, it may be best to judiciously administer ESAs targeted to hemoglobin levels between 10 and 12 g/dL (i.e., based primarily on recommendations included in the CKD guidelines) to informed cancer patients. However, stay tuned as new basic science knowledge emerges and clinical guidelines are updated, as these recommendations could change in the future.

References

1. Xue, JL.; Dalleska, F.; Murray, AM.; Collins, AJ. Cancer Prevalence in Patients with End-Stage Renal Disease. 2007 [accessed November 5, 2008]. Available at http://www.usrds.org/2005/pres/18U_asn_05_cancer_prevalence_in_pts_with_esrd.pdf
2. U.S. Food and Drug Administration. Drugs at FDA. 2007 November [accessed July 11, 2008]. Label. Available at <http://www.fda.gov/cder/foi/label/2007/103234s51581bl.pdf>
3. Morishita E, Masuda S, Nagao M, Yasuda Y, Sasaki R. Erythropoietin receptor is expressed in rat hippocampal and cerebral cortical neurons, and erythropoietin prevents in vitro glutamate-induced neuronal death. *Neuroscience*. 1997; 76:105–116. [PubMed: 8971763]
4. Mori S, Sawada T, Okada T, Kubota K. Erythropoietin and its derivative protect the intestine from severe ischemia/reperfusion injury in the rat. *Surgery*. 2008; 143(4):556–565. [PubMed: 18374054]
5. Nishiya D, Omura T, Shimada K, Matsumoto R, Kusuyama T, Enomoto S, Iwao H, Takeuchi K, Yoshikawa J, Yoshiyama M. Effects of erythropoietin on cardiac remodeling after myocardial infarction. *J Pharmacol Sci*. 2006; 101(1):31–39. [PubMed: 16717399]
6. Weber A, Dzietko M, Berns M, et al. Neuronal damage after moderate hypoxia and erythropoietin. *Neurobiol Dis*. 2005; 20:594–600. [PubMed: 15935685]
7. Druëke TB, Locatelli F, Clyne N, Eckardt KU, MacDougall IC, Tsakiris D, Burger HU, Scherhag A. CREATE Investigators: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006; 355:2071–2084. [PubMed: 17108342]
8. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D. CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006; 355:2085–2098. [PubMed: 17108343]
9. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998; 339:584–590. [PubMed: 9718377]
10. Food and Drug Administration Center for Drug Evaluation and Research Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. 2007 September [accessed July 18, 2007]. Available at <http://www.fda.gov/ohrms/dockets/ac/07/brie.ng/2007-4315b1-01-FDA.pdf>
11. Acs G, Acs P, Beckwith SM, Pitts RL, Clements E, Wong K, Verma A. Erythropoietin and erythropoietin receptor expression in human cancer. *Cancer Res*. 2001; 61:3561–3565. [PubMed: 11325818]
12. Henke M, Laszig R, Rube C, Schäfer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C, Frommhold H. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet*. 2003; 362:1255–1260. [PubMed: 14575968]
13. Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X, Vercammen E. 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(25):5960–5972. [PubMed: 16087945]
14. Henke M, Mattern D, Pepe M, Bezay C, Weissenberger C, Werner M, Pajonk F. Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol*. 2006; 24:4708–4713. Erratum in: *J Clin Oncol* 2007 Apr 10;25(11):1457. [PubMed: 17028293]

15. New Study Probes Safety of Erythropoiesis-Stimulating Agents. Medscape Medical News, June 10, 2008. [accessed July 11, 2008]. Available at <http://www.medscape.com/viewarticle/575670>
16. Blau CA, Miller CP, Lowe KA, Mattern D, Valliant-Saunders K, Urban N, Henke M. Predictive testing for erythropoietin induced tumor progression in head and neck cancer. *J Clin Oncol*. 2008; 26 abstr 11007.
17. Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, Barnato SE, Elverman KM, Courtney DM, McKoy JM, Edwards BJ, Tighe CC, Raisch DW, Yarnold PR, Dorr DA, Kuzel TM, Tallman MS, Trifilio SM, West DP, Lai SY, Henke M. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA*. 2008; 299:914–924. [PubMed: 18314434]
18. Glaspy, J.; Smith, R.; Aapro, M.; Ludwig, H.; Pinter, T.; Smakal, M.; Ciuleanu, T.; Chen, L. Results from a Phase III, randomized, double-blind, placebo-controlled study of darbepoetin alfa for the treatment of anemia in patients not receiving chemotherapy or radiotherapy. American Association for Cancer Research Annual Meeting Proceedings; April 14–28, 2007; Los Angeles, CA., 2007.
19. Oncologic Drugs Advisory Committee. Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia Associated with Cancer Chemotherapy. The Food and Drug Administration; 2007 May 10 [accessed July 29, 2008]. FDA briefing document. 2007. Available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf>
20. Oncologic Drugs Advisory Committee. FDA Briefing Document. 2008 March 13 [accessed April 11, 2008]. Available at <http://www.fda.gov/ohrms/dockets/ac/08/brief-ing/2008-4345b2-01-FDA.pdf>
21. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy-Induced Anemia. [accessed August 7, 2008]. V.1.2009. Available at http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf
22. Press Release. EMEA Recommends a New Warning for Epoetins for their Use in Cancer Patients. 2008 June 26 [accessed July 11, 2008]. Available at <http://www.emea.europa.eu/pdfs/human/press/pr/33396308en.pdf>
23. FDA Complete Response and Labeling Change Order, Epogen. 2008 July 30 [accessed August 12, 2008]. Available at http://www.fda.gov/cder/drug/infopage/RHE/epo_procrit/insertEpo.pdf
24. FDA Complete Response and Labeling Change Order, Aranesp. 2008 July 31 [accessed August 12, 2008]. Available at <http://www.fda.gov/cder/drug/infopage/RHE/aranesp/packageinsert.pdf>
25. Centers for Medicare and Medicaid Studies. Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions. [accessed August 7, 2008]. Issued January 2008, Effective November 2007. Available at http://www.cms.hhs.gov/manuals/downloads/ncd103c1_Part2.pdf
26. Kuenen BC, Rosen L, Smit EF, Parson MR, Levi M, Ruijter R, Huisman H, Kedde MA, Noordhuis P, van der Vijgh WJ, Peters GJ, Cropp GF, Scigalla P, Hoekman K, Pinedo HM, Giaccone G. Dose-finding and pharmacokinetic study of cisplatin, gemcitabine, and SU5416 in patients with solid tumors. *J Clin Oncol*. 2002; 20:1657–1667. [PubMed: 11896117]
27. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, Harousseau J, Zonder JA, Cavo M, Zangari M, Attal M, Belch A, Knop S, Joshua D, Sezer O, Ludwig H, Vesole D, Bladé J, Kyle R, Westin J, Weber D, Bringhen S, Niesvizky R, Waage A, von Lilienfeld-Toal M, Lonial S, Morgan GJ, Orlowski RZ, Shimizu K, Anderson KC, Boccadoro M, Durie BG, Sonneveld P, Hussein MA. International Myeloma Working Group: Prevention of thalidomide and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008; 22:414–423. [PubMed: 18094721]