# Treatment with erythropoiesis-stimulating agents in chronic kidney disease patients with cancer

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**Treatment of anemia remains an important component in the care of patients with nondialysis chronic kidney disease (CKD) and end-stage renal disease (ESRD). Erythropoietin-stimulating agents (ESAs) remains a key anemia treatment strategy in this patient population. However, anemia management in this group can become more complicated by prior or current history of malignancy. There has been a great deal of work both scientifically and in clinical trials in oncology that have revealed certain concerns and risks of ESA use in patients with cancer. In this review, we will bring together knowledge from nephrology and oncology literature to help nephrologists understand the implications for ESA treatment when CKD/ESRD is complicated by cancer. We also suggest an approach to the management of anemia in this patient group with active or previous malignancy.**

*Kidney International* advance online publication, 8 January 2014; doi:10.1038/ki.2013.528

KEYWORDS: anemia; chronic kidney disease; cancer; erythropoietin

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**Received 26 September 2013; revised 24 October 2013; accepted 24 October 2013**

Anemia remains an important complication of chronic kidney disease (CKD). Although several factors may have a contributing role in the development of anemia in CKD, the most important cause is an inappropriately low secretion of erythropoietin from the diseased kidneys. Erythropoiesis-stimulating agents (ESAs) continue to have an important role in the treatment of anemia in patients with CKD. ESA use in this group of patients has been shown to raise hemoglobin (Hgb) levels, decrease blood transfusion requirements, and improve the quality of life and symptoms related to anemia. However, normalization of Hgb levels in CKD patients has been associated with increased thromboembolic (cardiovascular and cerebrovascular) events. Studies reported in the oncology literature have also raised concerns regarding ESA safety, including an increased possible risk of cancer progression leading to poorer outcomes including increased mortality.

Anemia management may be challenging in a given advanced nondialysis CKD or end-stage renal disease (ESRD) patient who is found to have cancer. There are several management questions that arise. Currently, there are no guidelines for nephrologists regarding ESA and anemia management in CKD patients with previous or active cancer. This article will review the biology of erythropoietin with emphasis on the relationship with cancer. The current published literature on the subject will be discussed and clinical implications for ESA use in nondialysis CKD and ESRD patients with cancer will also be reviewed.

## ERYTHROPOIETIN BIOLOGY AND RELEVANCE FOR CANCER

Erythropoietin (Epo) is a 30.4-kDa glycoprotein hormone that is normally secreted by the adult kidney and the fetal liver.[1] Interstitial fibroblasts appear to be a major source of renal Epo synthesis.[2] The cellular recognition of tissue hypoxia and resultant stimulation of erythropoiesis start when tissue oxygen tension is decreased. This leads to stabilization of the transcription factor, hypoxia inducible factor-1,which then binds a site on the 3′ enhancer of the Epo gene that in turn leads to the upregulation of the gene and increased mRNA stability.[3,4] The Epo receptor (EpoR) is a 59-kDa peptide that is a member of the cytokine receptor family. When Epo binds to its receptor on the surface of erythroid progenitors, it

prevents cellular apoptosis. It also stimulates the proliferation and the terminal differentiation of cells committed to the erythroid lineage.[1] In addition to erythroid cells, there are other cell types that express the EpoR. Vascular endothelial cells, astrocytes and neurons, cardiac myocytes, retina and kidney, and mammary epithelial cells are some examples.[5] Different functions have been attributed to the EpoR in these cell types, although the nonerythroid function and purpose of Epo are not yet fully elucidated. Vascular endothelial cells express EpoR, and the interactions of Epo with its receptor have compounding effects. There are both *in vitro* and *in vivo* studies that show that the Epo–EpoR complex promotes proliferation, migration, and differentiation of normal endothelial cells into vascular tubes and hence the formation of new blood vessels. This process is driven by hypoxia and appears to be physiologic. However, it has been shown that this process may also be involved in pathological angiogenesis such as proliferative diabetic retinopathy.[6] Because of the importance of angiogenesis to tumors, the question naturally arises: do cancer cells express the EpoR, and if so are there clinical implications?

Initial evaluations for the EpoR on cancer cells tested either for the receptor protein itself or mRNA transcripts. The latter studies were probably less informative, as they examined EpoRmRNA levels from bulk tumor tissue, which may be contaminated by other cell types from blood or stromal tissue, thereby yielding potentially nonspecific results. Immunohistochemistry or western blotting with anti-EpoR antibodies were used for the analysis of EpoR protein. Initial reports indicated that the EpoR protein was found on certain tumor tissues.[7] Subsequent studies, however, found the antibodies used for testing to be nonspecific.[8] Liang *et al.*[9] have reported high levels of EpoR expression on breast cancer tissue using the anti-EpoR polyclonal antibody M-20. However, the demonstration that M-20 antibodies stained EpoR knockout tissue raised serious questions as to the validity of these findings.[10] Because of difficulties with anti-EpoR antibody specificity, other studies have focused instead on the functional response of cancer cell lines to EPO stimulation. These studies had conflicting results, but some did indicate a positive functional response.[11] However, even the positive studies lacked negative controls, and any functional response tended to be with molecules not part of the normal EPO signaling pathway, such as STAT5. The recent development of a first specific antibody to the EpoR (A82) with both positive and negative controls has allowed for a more rigorous method for testing for the EpoR protein on cancer cells.[12] In a study of 66 cancer cell lines, Swift *et al.*[13] found either no or very low levels of the EpoR protein. These more recent studies are important contributions; however, until they are confirmed by additional laboratories, the results cannot be taken as fully conclusive. Therefore, although the most recent data are pointing away from functional EpoR on cancer cells, the literature needs to mature further before definitive conclusions could be reached.

If EpoRs are found not to be present on most cancer cells, there still could be indirect effects of ESA treatment. Considerations would include the effect of supraphysiologic Hgb levels as used in most clinical trials, which would increase oxygen delivery to cancer cells and potentially stimulate proliferation. Another hypothetical indirect mechanism was described recently. When stimulated, macrophages express the EpoR. The binding of Epo to these cells can suppress NF-κB activation and proinflammatory genes, resulting in an immunosuppressive effect.[14] Such a mechanism could contribute to adverse effects during ESA treatment. Other indirect pathways have been discussed but would appear to be quite speculative at this point. However, the over-riding question is whether there truly is an effect of ESAs on cancer disease progression.

## LITERATURE ON ESA USE IN PATIENTS WITH CKD AND CANCER

Before examining the oncology literature, we first review the few nephrology studies that have evaluated cancer outcomes. ESAs have been widely used in the nondialysis CKD and ESRD patient population for several decades. ESAs have decreased the incidence of blood transfusions, improved symptoms related to anemia, and probably also improved patients' quality of life. However, randomized clinical trials have also identified cardiovascular risk with prolonged treatment with ESAs to Hgb targets higher than 13 g/dl. In addition, treatment to higher Hgb targets clearly increases the risk of thromboembolic events.

The Trial to Reduce Cardiovascular Events with Aranesp study was the first renal ESA trial to signal a relationship between ESA use and cancer mortality.[15] As it had the largest patient population studied and longest follow-up, it was the study best designed to find any possible cancer-promoting effect of ESAs. Although there was no significant difference in patients reporting a cancer-related adverse event (darbepoetin alfa group 6.9%, placebo group 6.4% ($P = 0.53$)), there was a trend towards increased risk of death attributed to cancer (darbepoetin alfa group, 39 deaths, placebo group, 25 deaths ($P = 0.08$)). Interestingly, an increased risk of death due to malignancy in patients with a previous history of cancer was also noted in the darbepoetin alfa group, with 14 of the 188 such patients assigned to darbepoetin alfa dying from cancer, as compared with one of the 160 patients assigned to placebo ($P = 0.002$).[15] These results raised concern as to adverse cancer outcomes with treatment to high Hgb targets for extended periods of time with ESAs.

Since the Trial to Reduce Cardiovascular Events with Aranesp, there have only been a few studies to evaluate ESA use in CKD patients with cancer. A Japanese study, Surveillance of Epoetin Adverse Events of Stroke and Cancer, in patients with CKD stages 4 and 5 failed to show an increased incidence of cancer.[16] The average Hb (10.1 g/dl), however, was relatively low in this study. It should also be noted that the trial had a very short surveillance time. A study by Seliger *et al.*[17] found an increased stroke risk in patients with CKD treated with ESAs. Interestingly, the increase in stroke risk applied only to CKD patients with a