Does Erythropoietin Promote Tumor Growth?

In Response: We appreciate Yoon and colleagues’ interest in our report and welcome the opportunity to reply to their comments. Our study was designed in a context in which several clinical trials, including patients with head and neck squamous cell carcinomas, breast cancer, non–small cell lung cancer and nonmyeloid malignancies, showed a potential deleterious effect of recombinant human erythropoietin on survival (1–6). A recently published meta-analysis of 57 randomized controlled trials that compared the use of recombinant human erythropoietin with a placebo indicated that treatment, compared with no treatment, was associated with a trend toward decreased survival (hazard ratio, 1.08; 95% confidence interval, 0.99-1.18; ref. 7). All these data prompted the Food and Drug Administration to release a Public Health Advisory bulletin including a boxed warning and additional labeling revisions that have been recently updated (8). Because so many patients receive recombinant human erythropoietin each year to improve their quality of life, it is therefore urgent to better understand the role of endogenous erythropoietin (EPO) and its receptor (EPOR).

In a preliminary study, we reported in a limited series of patients with non–small cell lung cancer that EPO/EPOR coexpression was frequent at both the mRNA and protein levels, confirming reports established in other solid tumors (9). We then believed that it was crucial to evaluate EPO/EPOR coexpression in tumor cells as a prognostic factor. Because our objective was to explore the role of EPO/EPOR coexpression in tumor cells, we chose patients with stage I non–small cell lung cancer to avoid confounding factors associated with advanced disease, the use of chemotherapy, and the potential use of recombinant human erythropoietin.

Yoon et al. point out the use of C-20 and H-162 polyclonal antibodies. In fact, the proposed experiment to test the specificity of available commercial antibodies.

Furthermore, to circumvent this potential lack of specificity, we considered high levels of EPO and EPO staining versus low levels of expression, and evaluated the effect of EPO/EPOR coexpression. Our blinded evaluation by two investigators (P. Callard and P. Saintigny) was highly reproducible. In our multivariate analysis, we showed that in this population, high levels of EPO expression and high levels of EPO/EPOR coexpression are independent prognostic factors for disease-specific survival. In other words, high levels of EPO/EPOR coexpression in 11% of our population was associated with a hazard ratio ~ 2 to die from the disease. Our interpretation is that it is very unlikely that nonspecific staining of both EPO and EPOR could give rise to such results. As discussed in our article, in at least two recent studies, EPOR gene overexpression appeared as a significant player of NSCLC behavior, thereby confirming its biological relevance (17, 18).

Yoon et al. claim that we mainly detected EPO and EPOR in the cytoplasm of tumor cells and that addressing the question of endogenous EPO/EPOR activity is crucial. We agree with this statement and evaluation of intracellular signaling is currently under investigation. In our previous work, we did not find any relation between EPO/EPOR coexpression and Ki67 staining (9). As in other nonhematopoietic cells, however, EPO might act in a tissue-protective manner and exert an antiapoptotic effect on tumor cells (18). Recent studies using recombinant soluble EPO, an anti-EPO monoclonal antibody, or a secreted EPO antagonist protein (EPOR) in ovarian and breast cancer models show an inhibition of tumor angiogenesis, an inhibition of cancer cell growth and of survival underlying a potential autocrine/paracrine role of secreted EPO on tumor cells and endothelial cells (19, 20). Functional preclinical work on patient-derived cell lines should help clarify this topic.

The potential dark side of erythropoietin in cancer cells has to be more deeply investigated (21). We believe that it would be more productive for all recombinant human erythropoietin stakeholders to help produce a highly specific monoclonal antibody against EPOR rather than highlighting the lack of specificity of available commercial antibodies.

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