Letter to the Editor

Efficacy of Zibotentan in Colorectal Cancer—Letter

Panagiotis J. Vlachostergios

In their study, Haque and colleagues evaluate the specific endothelin A receptor (ETAR) antagonist zibotentan in colorectal cancer cellular models with relevance to proliferation and migration potential of tumor cells and stromal fibroblasts. Interestingly, they demonstrate that ETAR is the principal receptor used by ET-1 and provide evidence for involvement of stromal fibroblasts in cancer progression as targets of ET-1 signaling. Given zibotentan had the greatest inhibitory effect on ET-1 signaling, the authors suggest a potential role of the drug in adjuvant therapy of colorectal cancer (1). These data are further confirmed by more recent evidence that ET-1 signaling through ETAR promotes liver metastasis in colorectal cancer (2).

The model of aberrant ET-1 signaling in colorectal cancer seems to share many similarities with that of prostate cancer, given the endothelin axis has also been implicated in progression from androgen-sensitive to androgen-independent state (3). However, it remains elusive why encouraging preclinical data on zibotentan were not replicated at the clinical level about prostate cancer treatment. This was not only observed in the metastatic but also in the nonmetastatic setting (4).

Notably, in addition to ETAR, ET-1 mediates its signaling effects through transactivation or direct activation of several pathways, such as PI3K/Akt, contribution of which is often underscored at the preclinical level (5).

Thus, a consideration for specific ET-1 inhibition rather than ETAR antagonism might be more reasonable in terms of achieving a wider targeting of ET-1 signaling. In addition, several factors that interfere with ET-1 signaling within the tumor microenvironment, such as intratumoral hypoxia, are not taken into account when designing targeted treatments. In that perspective, a combined strategy might be more successful in establishing more efficient inhibition of the endothelin axis.

Another issue that remains to be answered is identification of a surrogate marker of response for this targeted treatment. Previous testing of serum ET-1 levels or plasma big ET-1 in patients with colorectal cancer has not yielded consistent results about their prognostic or predictive value (6). This might at least partially be attributed to their non–cancer-specific association with hypertension. Finally, little is known about the effect of antiangiogenic and/or anti–EGFR-targeted treatments on ET-1 signaling at the colorectal cancer metastatic setting.

It would, therefore, be interesting to see whether the failure of zibotentan to provide significant improvement in overall survival of patients with prostate cancer is replicated or not in the case of colorectal cancer. Results from the ongoing phase II study of zibotentan added to FOLFIRI for patients with metastatic colorectal cancer are eagerly awaited. Notably, given preclinical implications for an antimetastatic role of zibotentan (1, 2), the design of a study testing the drug in the adjuvant setting as an adjunct to established regimens would also be helpful to decipher whether intervention to the endothelin axis in colorectal cancer may actually delay relapse of disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received October 3, 2013; revised December 5, 2013; accepted December 12, 2013; published OnlineFirst May 16, 2014.

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