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).

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