Efficacy of Zibotentan in Colorectal Cancer—Response

Samer-ul Haque, Hazel Welch, Michael Dashwood, Bala Ramesh, and Marilena Loizidou

Panagiotis Vlachostergios highlights the importance of evaluating clinically the targeted therapeutic zibotentan.

Despite the wide overexpression of endothelin-1 (ET-1) and endothelin A receptors in the majority of carcinomas (1), establishing clinical efficacy of receptor antagonism has proved complex. Numerous factors predispose to discrepancies between preclinical data and clinical outcomes, such as evaluating antagonists in "isolated" cancer cell line cultures. Recently, interest has grown in evaluating drugs within more complex environments involving signaling pathways associated with stromal components: cancer-associated fibroblasts and neovascularization. The importance of fibroblasts in cancer was highlighted many years ago (2).

Our group further defined, at mRNA and protein levels, how exposure to and antagonism of ET axis molecules affected both cancer cells, which define cancer parenchyma, and fibroblasts, which populate and refashion cancer stroma. Specifically, zibotentan treatment opposed antiapoptotic pathways, invasive and neovascularization properties, and reduced chemoresistance (3). This we believe justifies its use as additional first-line therapy and points to multitherapy agents for targeting colorectal cancer.

To overcome limitations of two-dimensional (2D) cultures, we recently developed a three-dimensional (3D) tissue-engineered in vitro cancer model with distinct compartments (cancer and stroma) that exhibits central hypoxia (4); we are currently developing this as a platform technology for drug testing. Recent studies demonstrate that MCF7 breast cancer cells in 3D collagen I matrices have an altered (reduced) phosphoinositide 3-kinase (PI3K) pathway response when exposed to chemotherapeutics, compared with 2D models (5). Hence, moving to 3D models may present us with more relevant laboratory models for drug evaluations.

Clinical trials often start at advanced stages of disease or following previous therapies. This may lead to altered drug-induced molecular signaling away from classic tumorigenic pathways (studied laboratory settings), drug resistance via MDR upregulation, switching high-dimensional cancer attractors, more aggressive dedifferentiated tumors, and resilient types due to Darwinian selection or Lamarckian induction.

In terms of molecular mechanisms, we demonstrated in colorectal cancer cells that ET-1 activates numerous tumorigenic signal transduction mechanisms, including PI3K. Inhibiting ET-1 is an initially attractive option; however, this inhibition may result in detrimental systemic effects, especially within vascular beds causing hypotension, renal, and neurologic dysfunction.

We are considering interfering RNA approaches integrated in a nanodrug delivery platform, carrying multiple anticancer agents. We suggest that this approach may optimize targeted delivery while effectively targeting multiple pathways.

In terms of markers of response, we agree that ET axis molecules are inappropriate; therefore, more conventional markers need to remain in use. However, this does not detract from their usefulness as targets for treatment. We are also looking forward to the results from the ongoing clinical trials.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Received January 7, 2014; revised February 10, 2014; accepted March 4, 2014; published OnlineFirst May 16, 2014.

References
Molecular Cancer Therapeutics

Efficacy of Zibotentan in Colorectal Cancer—Response
Samer-ul Haque, Hazel Welch, Michael Dashwood, et al.


Updated version Access the most recent version of this article at:
doi:10.1158/1535-7163.MCT-14-0002