Letters to the Editor

Targeted Therapeutics in Pancreatic Cancer: A Ray of Hope

To the Editor: We greatly appreciate the thoughtful comments by Sauder et al. concerning the potential complications that may be associated with therapies directed at vascular endothelial growth factor (VEGF) signaling pathways (1), and we are grateful to them for their interest in our article dealing with VEGF-Trap and its potential usefulness in pancreatic cancer (2). Indeed, several novel therapies in the relatively new field of targeted therapeutics either have been approved for clinical use or are making their way from the bench to the bedside. Yet, it is increasingly evident that such therapies, although capable of producing dramatic results in some cases, may also be associated with specific side effect profiles that will require our continued vigilance with respect to target selection and drug design and with respect to unintended harmful consequences.

In animal models, complications associated with the suppression of VEGF-dependent pathways have included proteinuria associated with either anti-VEGF antibodies or soluble VEGF receptor (VEGFR)-1 (3), emphysema associated with inhibition of VEGFR kinase activity by SU5416 (4), liver disease as a result of adenovirus-mediated delivery of soluble VEGFR-1 (5), and, as noted by Sauder et al. using NZB/W mice, acceleration of the onset of glomerulonephritis and glomerulosclerosis (1). In addition to the renal disease, they observed an increasing incidence of ascites and edema and a progressive and dramatic increase in mortality (1). These are important observations that must command our attention when considering the use of therapies targeted at blocking VEGF actions in humans.

It is well established that the loss of a single VEGF-A allele in mice results in impaired angiogenesis, severe developmental anomalies, and embryonic lethality, underscoring the importance and tight dose-dependent regulation of embryonic vessel development by VEGF-A (6). VEGF-A is also required for cyclical blood vessel proliferation in the female reproductive tract, for ulcer healing, and for longitudinal bone growth and endochondral bone formation in postnatal development (7). Given the important role of VEGF-A in embryogenesis as well as in tissue remodeling and repair, it is possible that the use of young mice (6-8 weeks old) that have a genetic susceptibility to renal disease, in conjunction with the administration of the anti-VEGFR-2 antibody every third day for 24 weeks, resulted in the above serious complications. By contrast, the mice in our study, although of similar age, were treated with VEGF-Trap for only 6 weeks. We did not observe ascites or edema in any of the mice harboring s.c. tumors (2). Instead, in our metastatic model, two of six mice exhibited tumor associated ascites, whereas none of the mice treated with VEGF-Trap developed ascites, indicating that suppression of VEGF-A-dependent pathways attenuates a tumor-associated propensity toward ascites development. Moreover, although most of the mitogenic effects of VEGF-A toward endothelial cells are believed to occur via VEGFR-2, VEGF-A also activates the related VEGFR-1. It is conceivable, therefore, that VEGFR-2 targeting by the DC101 antibody may spare VEGFR-1, thereby resulting in a signaling imbalance and complications that are distinct from those that may be induced by VEGF sequestration.

Important information with respect to the potential complications of VEGF targeted therapeutics can be gleaned from results observed during clinical trials with the anti-VEGF antibody bevacizumab. In a recent study in patients with metastatic renal cancer (8), two different doses of bevacizumab were administered to 37 (3 mg/kg) and 39 (10 mg/kg) patients, with a median follow-up time from study entry of 27 months. The most frequent complications were hypertension and proteinuria, and the hypertension was most often responsive to standard antihypertensive therapy (8). Additional complications in this study included malaise, epistaxis, fever, mildly elevated alanine aminotransferase levels, and hyponatremia. There were no life-threatening toxic effects or deaths that could be attributable to the drug in this study, although 68 of these patients had undergone a nephrectomy, and all patients exhibited disease progression before study entry. Although these observations are reassuring, they do not mitigate against heeding the concerns raised by Sauder et al., and it would indeed be prudent to exercise caution when considering anti-VEGF therapy in patients with renal disease or in patients who are taking nephrotoxic drugs.

Our article focused on the potential usefulness of VEGF-Trap in pancreatic cancer, a deadly malignancy that is characterized by a high frequency of K-ras, p53, p16, and Smad4 mutations and with an overexpression of many mitogenic growth factors (9). Although many of these growth factors are also angiogenic (9), conditioned medium from pancreatic cancer cells fails to exhibit angiogenic activity in the presence of neutralizing anti-VEGF-A antibodies, suggesting that it is the major angiogenic factor produced by these cells (10). The importance of VEGF-A is further underscored by its abundance in the cancer cells within human pancreatic carcinomas and by its expression in the adjacent stromal fibroblasts (11). These observations raise the possibility that VEGF-Trap, whose affinity toward VEGF-A is in the pM range (12) and other interventions that efficiently target VEGF pathways, may lead to novel therapeutic options in pancreatic cancer.

In should now also be possible to combine antiangiogenic agents with therapies that are directed at other excessively or aberrantly activated pathways. For example, the epidermal growth factor receptor and its ligands are overexpressed in a high proportion of pancreatic cancers, and the combined use of anti-VEGF and anti—epidermal growth factor receptor strategies may further improve outcome. Given the current dismal prognosis for patients with pancreatic cancer, the possibility of devising novel “targeted” therapies rather than relying on current chemotherapeutic approaches represents a new ray of hope for these patients.
REFERENCES


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