EDITORIAL

LIMITS OF ANTI-ANGIOGENIC THERAPY

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Angiogenesis is controlled by the balance between molecules that have positive and negative regulatory activities and this concept has led to the notion of the angiogenic switch, which depends on an increased production of one or more positive regulators of angiogenesis [1]. Most human tumors arise and remain in situ without angiogenesis for a long time before switching to an angiogenic phenotype, through a pre-neoplastic stage as occurs in breast and cervical carcinomas, which becomes neovascularized before the malignant tumor appears. Activation of the angiogenic switch has been attributed to the synthesis or release of angiogenic factors, and accordingly to the balance hypothesis, the level of angiogenesis inducers and inhibitors regulates angiogenesis in physiological conditions. This balance is altered in pathological conditions, including tumors, as a consequence of an increase bioavailability or activity of the inducer proteins, or reducing the concentrations of endogenous angiogenesis inhibitors. Restore of this balance may induce a normalization of structure of blood vessels. The concept of "normalization" of tumor blood vessels by anti-angiogenic drugs was introduced by Rakesh Jain in 2001 [2]. Accordingly, anti-vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) therapies induce morpho-functional normalization of tumor blood vessels, favoring an increase in blood flow and release of cytotoxic drugs. However, in non small cell lung cancer (NSCLC) anti-angiogenic therapy decreases cytotoxic drug delivery to tumors [3]. The state of normalization is probably transient and dependent on the dose and duration of the treatment.

Beginning in the 1980's, the industry exploited the field of anti-angiogenesis for creating new therapeutic molecules in angiogenesis-dependent diseases. However, experimental drugs that in preclinical early stage prevention or intervention trials have been proven to efficiently impair the onset of tumor angiogenesis may not exert any anti-angiogenic activity when tested in late stage intervention or regression trials, as usually performed in the clinics.

At present anti-angiogenic therapy is essentially anti-VEGF)/VEGFR therapy and has yet fulfilled its promise in the clinic. Bevacizumab (Avastin) was the first angiogenesis inhibitor approved by the Food and Drug Adminstration (FDA) for the treatment of colorectal cancer in February 2004, administered in combination with irinotecan, 5-fluorouracil and leucovirin [4]. It was subsequently approved for use, in combination with cytotoxic chemotherapy, in other cancers. Actually, inhibition of VEGF/VEGFR axis is obtained by targeting VEGF ligand with antibodies or receptor traps, or its receptors with small-molecule tyrosine kinase inhibitors (TKI). Clinical benefits are obtained when ligand-blocking drugs are combined with chemotherapeutic agents or radiotherapy, while clinical studies testing various TKIs combined with chemotherapy have failed because of increased cytoxicity.

Depending on cancer type, these anti-angiogenic treatments can lead to a 3-6 months increase in progression-free survival, but fail to provide enduring clinical responses, with transitory improvements being followed by a relapse phase in tumor angiogenesis and subsequent tumor growth.

Removal of VEGF inhibition causes tumor re-growth due to the fact that pericytes provide a scaffold for the rapidly re-growing of tumor vessels [5]. The occurrence of pericytes expressing alpha smooth muscle actin (α-SMA) has been considered as a biomarker for tumors refractory to therapy [6]. Pericytes have been indicated as putative targets in the pharmacological therapy of tumors by using the synergistic effect of anti-endothelial and anti-pericytic molecules. Removal of pericyte coverage leads to exposed tumor vessels, which may explain the enhanced effect of combining inhibitors that target both tumor vessels and pericytes. Bergers et al. (2003) showed that combined treatment or pre-treatment with anti-platelet derived growth factor (PDGF-B)/platelet derived growth factor receptor beta (PDGFBR-β) reducing pericyte coverage increases the success of anti-VEGF treatment in the mouse RIP1-TAG2 model [7]. PDGFR inhibition has been developed

in the context of combined inhibition of VEGFR and PDGFR with dual-specificity small-molecule inhibitors, including sunitinib, sorafenib, and pazopanib.

The results from clinical trials have not shown the dramatic antitumor effects that were expected following preclinical studies, which revealed a much higher efficacy of these type of agent in animal models. Patients with different types of tumors respond differently to anti-angiogenic therapy. While colorectal, lung and breast cancer patients have responded, pancreatic cancer patients have not shown survival advantages when treated with anti-angiogenic monotherapy or combinations of anti-angiogenic agents with chemotherapy. Moreover, responses to anti-angiogenic drugs vary between primary tumors and their metastases [8].

Additionally, preclinical and clinical data have shown the possibility that tumors may acquire resistance to anti-angiogenic drugs or may escape anti-angiogenic therapy via compensatory mechanisms. Most of the FDA-approved drugs, as well as those in phase III clinical trials, target a single pro-angiogenic protein. However, multiple angiogenic molecules may be produced by tumors, and tumors at different stages of development may depend on different angiogenic factors for their blood supply. Therefore, blocking a single angiogenic molecule might have little or no impact on tumor growth. In 2011, it has been introduced the use of dual fibroblast growth factor receptor (FGFR)/VEGF TKI brivanib, that inhibits VEGFR1-3 and disrupt FGFR1-3, overcoming resistance to VEGF-selective therapy, and blocking FGF-dependent tumor proliferation [9].

Finally, it has been demonstrated that angiogenesis inhibitors make some tumors more aggressive in different animals, increasing invasion and lymphatic or hematogeneous metastasis [10,11].

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