EDITORIAL

Overview of Antiangiogenic Therapies in Hematological Malignancies

It has been generally accepted that angiogenesis is involved in the pathogenesis of hematological malignancies, like acute and chronic leukemia, lymphoma, myelodysplastic syndromes, myeloproliferative neoplasms, and multiple myeloma. The extent of angiogenesis in the bone marrrow has been correlated with disease burden, prognosis, and treatment outcome [1].

Reciprocal positive and negative interactions between tumor cells and bone marrow stromal cells, namely hematopoietic stem cells, fibroblasts, osteoblasts/osteoclasts, endothelial cells, endothelial progenitor cells, T cells, macrophages and mast cells, mediated by an array of cytokines, receptors and adhesion molecules, modulate the angiogenic response in hematological tumors [2]. More recently, it has been emphasized the pro-angiogenic role of the so called "vascular niche", indicating a site rich in blood vessels where endothelial cells and mural cells such as pericytes and smooth muscle cells create a microenvironment that affects the behavior of several stem and progenitor cells, in hematological malignancies [3].

The pivotal role of autocrine vascular endothelial growth factor (VEGF) loops in hematological malignancies has been confirmed by the coexpression of both VEGF and VEGF receptors (VEGFRs) in leukemia, lymphoma, and multiple myeloma coupled with direct effects on tumor cell survival, migration, and proliferation [4].

Antiangiogenesis was proposed as a cancer therapy over 30 years ago, when J. Folkman published in the *New England Journal of Medicine* a hypothesis that tumor growth is angiogenesis-dependent [5]. He hypothesized that tumors would be unable to grow beyond a microscopic size of 1 to 2 mm^3 without continuous recruitment of new capillary blood vessels and introduced the concept that tumors probably secreted diffusible molecules that could stimulate the growth of new blood vessels toward the tumor and that the resulting tumor neovascularization could conceivably be prevented or interrupted by drugs called angiogenesis inhibitors [5].

Few angiogenesis inhibitors would ever be found before 1980, when the biopharmaceutical industry began exploiting the field of antiangiogenesis for creating new therapeutic compounds for modulating new blood vessel growth in angiogenesis-dependent diseases until February 2004, when the US Food and Drug Administration (FDA) approved bevacizumab, a humanized anti-VEGF-A monoclonal antibody for the treatment of metastatic colorectal cancer in combination with 5-fluorouracil (FU)-based chemotherapy regimens [6].

A plethora of new antiangiogenic treatment approaches for patients affected by hematological tumors has emerged in recent years. Antiangiogenic therapies are mostly based on inhibiting the binding of VEGF to VEGFRs by neutralizing antibodies to the ligand or to the receptor, soluble receptors, small molecule inhibitors or are directed against the tyrosine kinase activity of the VEGFRs.

Angiogenesis inhibitors can act as a two edged sword, because although they inhibit angiogenesis, they may also induce tumor re-growth and favour metastatic process [7]. In particular, the responses to antiangiogenic agents targeting VEGF are commonly transient, suggesting that there are effective escape mechanisms for blood vessel formation, and for this reason it has been suggested that anti-VEGF therapy is most effective when combined with chemotherapy or radiotherapy [8]. When chemotherapy is used in a conventional manner (i.e. bolus drug administration followed by a 3-4 week drug-free period to allow the host to recover from adverse side effects), the vascular damage is rapidly repaired during the recovery period. Browder *et al*. [9] showed that by shortening the drug-free break period, the antiangiogenic effect of cytotoxic drugs can be augmented, and this form of antiangiogenic chemotherapy, referred as metronomic chemotherapy [10], is more potent when combined with drugs that interfere with the endothelial cell survival activity of VEGF [11]. There is emerging evidence that VEGF-A may be replaced by other angiogenic pathways as the disease progress: higher amounts of fibroblast growth factor-2 (FGF-2) were detected when the VEGF pathway was blocked in mice [12] and an analysis of human breast cancer biopsies revealed that late stage breast cancers expressed a plethora of pro-angiogenic factors in contrast to earlier stage lesions, which preferentially expressed VEGF [13].

Another mechanism that can circumvent the antiangiogenic therapy is the recruitment of bone marrow-derived hematopoietic progenitor cells (HPC) and endothelial progenitor cells (EPC), both of which can obviate the necessity of VEGF signaling and can stimulate vasculogenesis in tumors [14-16]. Finally, anti-VEGF-VEGFRs therapies cause a number of side effects and the toxicities imply that angiogenesis is a multi-factorial biological process that involves various pathways in the body, such as the coagulation cascade, the immune system and blood flow regulation.

Several preclinical and clinical trials are exploring the combination of various angiogenesis inhibitors with other targeted therapies, such as epidermal growth factor receptor (EGFR) or Her 2 inhibitors (cetuximab, erlotininb and trastuzumab), platelet derived growth factor receptor (PDGFR)/ber-abl inhibitors (imatinib), proteasome inhibitors (bortezomib) and other antiangiogenic agents such as inhibtors of integrins.

In conclusion, even if exciting results have been obtained in preclinical studies, they have been rarely confirmed in the clinical setting, in which angiogenesis inhibitors showed to prolong progression-free survival, but had only small effects on overall survival and as there are still cases in which the remissions are partial or patients develop resistance to the treatment, other antiangiogenic drugs that block the interaction of VEGF with its receptors, or acting as tyrosine kinase inhibitors, or indirectly inhibiting VEGF remains to be developed.

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