PHARMACOLOGICAL MODULATION OF CHEMOTHERAPY EFFICACY BY ANTIANGIOGENIC DRUGS

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One of the most significant recent developments in medical oncology has been the approval of a number of antiangiogenic drugs for the treatment of a variety of cancers. These drugs include bevacizumab (Avastin®), the monoclonal anti-VEGF antibody, and two oral small molecule receptor tyrosine kinase inhibitors (RTKIs) which block VEGF and other growth factor signaling RTKs, eg. sunitinib (Sutent®) and sorafenib (Nexavar®). Whereas the latter two drugs have been approved as single agent therapies for renal cell cancer, bevacizumab has been approved for the treatment of colorectal and non small cell lung cancer when combined with certain standard chemotherapy regimens. A number of phase II clinical trials have also shown that bevacizumab brings about a clinical benefit in advanced disease primarily, or only, when it is combined with chemotherapy.

The ability of an antiangiogenic drug such as bevacizumab to increase the efficacy of chemotherapy would seem counterintuitive since this type of drug is designed to reduce tumor vascularity, and compromise blood flow/perfusion, thus starving tumors of oxygen and making them more hypoxic. Hypoxia is known to be a major mechanism of radiation and chemo-resistance. Several mechanisms have been proposed to account for the chemosensitizing efficacy of antiangiogenic drugs (1). One such theory, which we have been actively investigating, relates to the ability of antiangiogenic drugs to suppress, or block, proangiogenic/vasculogenic “rebounds” induced by chemotherapy which may accelerate tumor cell repopulation. For example, administration of certain cytotoxic drugs such as “vascular disrupting agents” (VDAs) can cause an acute and marked mobilization of cells resident in the bone marrow, which can then enter the peripheral blood circulation, and home to sites of tumor growth (2). Some of these cells can then become incorporated into the lumens of growing tumor blood vessels and differentiate into endothelial cells thus promoting tumor angiogenesis and tumor growth (2). These are called circulating endothelial progenitor cells (CEPs). However, combination therapy with an antiangiogenic drug such as a VEGF receptor blocking antibody can effectively block this therapy induced acute CEP mobilization. We now have evidence that certain chemotherapy drugs administered at maximum tolerated doses (MTDs) can also cause CEP rebounds, which can be blocked by concurrent treatment with an antiangiogenic drug. As a result, we speculate that the anti-tumor effects of chemotherapy can be enhanced by antiangiogenic drugs, by virtue of blocking this potentially tumor growth promoting effect and slowing down tumor cell repopulation between successive cycles of MTD chemotherapy.

References:

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