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Short Communication

Antiangiogenic Therapy: Issues and Expectations

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DESCRIPTION

The understanding that angiogenesis is essential for tumor growth and metastasis formation has led to a large effort to discover effective antiangiogenic compounds [1]. It should be perceived that angiogenesis happens in pathologic cycles as well as in homeostasis. Physiologic angiogenesis is significant in multiplication, wound healing, menses, and vascular diseases like coronary artery and peripheral vascular diseases. Thus, as always, a balance must be maintained between limiting angiogenesis to the tumor and causing significant toxicity to the host. In addition to the potential toxicity, another issue in antiangiogenic therapy is the chronic nature of this therapy. Because antiangiogenic therapy is designed to inhibit the development of new blood vessels, the end points for success or failure must be redefined. For example, a desired response to standard chemotherapy is one that decreases the cross-sectional area of a tumor by 50% within a few months.

However, antiangiogenic therapy is probably going to create stable infection, which almost immediately might be considered a failure. Thus, in evaluating antiangiogenic therapy in the clinic or the laboratory, different criteria for effectiveness must be outlined [2]. Because antiangiogenic therapy may not decrease tumor growth, it is likely that this therapy will need to be delivered on a chronic basis. Hence, the agent must be easily delivered (i.e., oral) and have few long-term side effects. One must also consider that the effect of antiangiogenic therapy may require a longer interval between evaluations than does chemotherapy, as the stability of disease may be difficult to determine at short intervals. There have, of course, been reports of complete regression of tumors in experimental models of angiogenesis. However, these reports are few, and the vast majority of studies in this field have demonstrated that antiangiogenic therapy leads to an inhibition of tumor growth. Thus, it is critical that the reader be able to interpret experimental studies appropriately and avoid creating unrealistic expectations. For example, the sites of tumor injection must be considered when experimental antiangiogenic studies are being conducted [3]. It is clear that endothelia from different organs are phenotypically distinct and that therapy effective at one site may be ineffective at another site. In addition, the growth and patterns of metastases depend on the site of injection.

Thus, the most relevant model for evaluating antiangiogenic therapy is an orthotopic model in which the tumor is growing in the appropriate host environment. Moreover, in designing experiments or reading the literature, it is important to determine whether antiangiogenic therapy is being designed as (1) a chemopreventive agent (delivered prior to or at the time of tumor inoculation), (2) adjuvant therapy (delivered when the tumor is at a relatively small volume, such as shortly after tumor injection), or (3) a therapeutic modality (delivered to animals with established tumors). In evaluating responses to antiangiogenic therapy, one must define the end points prior to initiation of the study. Typically, tumor size or mass is determined at initiation of therapy and at termination of the study. As a surrogate means of assessing drug activity, biopsies of accessible tumors can be obtained for immunohistochemical staining to determine vessel counts, tumor cell proliferation and apoptotic rates, and endothelial cell proliferation and apoptotic rates. More important, survival studies may better assess the effectiveness of antiangiogenic therapy [4].

Preclinical data suggest that the efficacy of a conventional cytotoxic drug can be improved by combination with an angiogenesis inhibitor. Indeed, a number of antiangiogenic clinical trials currently in progress have been designed to compare the effects of a particular cytotoxic agent alone with the effects of the same agent in combination with an angiogenesis inhibitor. Clearly, the success of Herceptin in improving the effects of cytotoxic chemotherapy in a proportion of advanced-stage breast cancer patients has enhanced the credibility of this strategy of evaluating cytostatic drugs. This could allow conventional end points, such as tumor shrinkage and prolonged survival of very sick patients, to be used, albeit indirectly, as a convenient means of more rapidly assessing the merit of antiangiogenic drugs. Another possible approach to effect tumor vascular growth could be the increased use of improved antivascular targeting strategies that can cause acute tumor regression, as shown in various preclinical models. For example, certain tubulin-binding agents, such as combretastatin A-4, can cause such an effect, as can antibodies that target tissue

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factor to newly formed blood vessels, thus causing an intravascular thrombogenic response in such vessels [5]. These drugs kill endothelial cells of newly formed blood vessels by different mechanisms that result in vascular collapse and the subsequent death of much larger numbers of tumor cells. Clearly, the problem here will be to develop drugs that have this ability to cause such a dramatic tumor infarction without major, perhaps even life-threatening, toxic side effects.

In this regard, a potentially significant development in the near future could be the use of genomics-based technologies to uncover a large number of highly (or even totally) specific molecular markers for the activated endothelial cells of newly formed blood vessels. This could make antibody-based therapeutics safer and more effective. Cytostatic antiangiogenic agents have the desired biologic (i.e., antiangiogenic) effect *in vivo*. In experimental animal models, tumors can be respected and analyzed for such changes as the extent of vascularization, vascular structure, and endothelial cell viability or apoptosis as well as for markers of angiogenic activity (e.g., expression of VEGF, bFGF, IL-8) [6].

CONCLUSION

Performing serial biopsies of metastatic tumors will not be practical; thus, reliable surrogate markers of tumor angiogenesis found in serum or urine may be necessary. At present, few, if any such markers (at least of a reliable nature) exist. The use of noninvasive medical imaging strategies (e.g., magnetic resonance imaging, Doppler ultrasound) to monitor changes in tumor blood flow, vascular structure, and permeability may be helpful, and considerable research efforts to determine their efficacy are under way.

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