New and Newer Vascular Targets in Oncology

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This review covers progress to date in the identification of molecular targets on blood vessels in cancers, as well as agents that act on those targets, with emphasis on those currently in clinical trials. Current vascular-targeting therapies comprise two general types—antiangiogenic therapy and antivascular therapy. Advances in antiangiogenic therapies, particularly inhibitors of vascular endothelial growth factors and their receptors, have clarified the capacity of these inhibitors to change tumor-associated vessel structure to a more normal state, thereby improving the ability of chemotherapeutics to access the tumors. The responses of other antiangiogenesis target molecules in humans are more complicated; for example, $\alpha_v\beta_3$ integrins are known to stimulate as well as inhibit angiogenesis, and cleavage of various extracellular proteins/proteoglycans by matrix metalloproteinases produces potent regulators of the angiogenic process. Antivascular therapies disrupt established blood vessels in solid tumors and often involve the use of ligand-based or small-molecule agents. Ligand-based agents, irrespective of the antiangiogenic capacity of the ligand, target antivascular effectors to molecules expressed specifically on blood vessels, such as aminopeptidase N, fibronectin extra-domain B, and prostate-specific membrane antigen. Small-molecule antivascular agents, which are not targeted to molecules on blood vessels, rely on physical differences between the vasculatures in tumors and those in normal tissues.

In this review by Sato et al, the authors outline translational research on molecular targets in the field of antiangiogenic and antivascular treatment. Given the recent clinical successes seen with such treatment, we have a wealth of new therapies on the horizon and it is helpful to see those novel and complicated treatments outlined in an organized manner. The authors have chosen to separate antiangiogenic therapy and antivascular therapy. While this is quite helpful in a structured discussion of targets, it is important to realize that the major success stories thus far in clinical practice have involved agents with potential effects on both angiogenesis and established blood vessels as well as direct interaction with tumor cell receptors. As stated in their abstract, the authors have attempted to focus their discussion around targets with agents available in current clinical trials. In addition, they mention some of their own exciting preclinical data affecting targets such as integrins and matrix metalloproteinases, which have not yet translated into clinical trials. Although these targetable receptors or ligands are scientifically valid and may show preclinical signals of success, the majority are either in early-stage development or have led to disappointments in the clinic, as the authors note. Since it is unknown what the future has in store for these agents and targets, we have attempted to put these bench-to-bedside novel therapeutics in the clinical context of late-stage and approved agents. In addition, we choose to highlight our own work with anti–prostate-specific membrane antigen (PSMA) antibodies as an example of bench-to-bedside work in antivascular therapy.

Recent Clinical Successes: Lessons Learned With School Still in Session
In recent years, several phase III clinical trials have demonstrated the utility of antiangiogenic treatment. In particular, bevacizumab (Avastin), a monoclonal antibody against vascular endothelial growth factor (VEGF), has been shown to be effective in combination with cytotoxic chemotherapy in metastatic colorectal, lung, and breast cancer. In addition, orally administered multitargeted tyrosine kinase inhibitors given as single agents (namely sunitinib [Sutent] and sorafenib [Nexavar]), have been shown to be effective in metastatic renal cell carcinoma, gastrointestinal stromal tumors, and hepatocellular carcinoma. Along with several phase I and II studies, these trials have definitively established that antiangiogenic therapies can be an additional tool in our treatment of advanced cancer. These early and clear successes have paved the road for further novel antiangiogenic therapies, as outlined in this review. As we advance our understanding of tumor angiogenesis, our treatments will evolve as well. However, as new treatments are added to our therapeutic armamentarium, significant unanswered questions remain.
While it is difficult to argue with the clinical success of recent trials, they have not come without significant side effects. The addition of bevacizumab to cytotoxic chemotherapy seems to increase the incidence of arterial thromboembolic events.[1] In addition, preliminary evidence of severe hemorrhagic toxicities has led to caution regarding use of these agents in subsets of patients or histologies. New toxicities such as hypertension and proteinuria have emerged. Some toxicities may be due to increased cytotoxic drug delivery, others due to class effects of antiangiogenic therapy, and others due to "off-target" effects.

Additional work needs to be done with the currently available antivascular treatments to potentially improve their efficacy and minimize their toxicity. Antiangiogenic treatment targets cancer in an untraditional way, attacking tumor vasculature rather than tumor cells themselves. Some target ligands of important receptors rather than individual tumor cells or their vasculature. Optimal dosing and schedules of administration remain to be defined. The traditional phase I dose-escalation trials aimed at defining a maximal tolerated dose to use in phase II trials may not be the best approach. In the era of "targeted" therapy, biologic or physiologic endpoints may be more important in defining the optimal regimens. Traditional assessments such as response rates calculated via decreases in sums of uni- or bidimensionally measured tumors on radiographs may not be as important as survival and quality-of-life outcomes. In addition, an optimal dose and schedule in one tumor type or host may be suboptimal in others. Combinations of antiangiogenic therapy plus cytotoxic therapy have proven to be useful. Combinations of two or more antiangiogenic or antivascular agents may be useful as well, but we will need to be wary of toxicities and cost. Further investigation into the optimal sequencing of these agents or their use with traditional chemotherapeutics may be a further strategy to improve efficacy. All of the mature data to date have been in the advanced disease setting, and no cures have been consistently reported. Investigations in the minimal residual disease setting such as traditional adjuvant therapy may prove to have the greatest impact in the future. We await the completion of the Eastern Cooperative Oncology Group-led trial (ECOG 2805) as an excellent example of testing this concept.

**PSMA: Its Role in Prostate Cancer and Other Tumors**

Because of the observed improvements in survival and the significant side effects noted with current antiangiogenic treatment, a considerable volume of research is dedicated to developing the next generation of antivascular treatment. As Sato et al state, one goal of current research is to target not only angiogenesis but the tumor vasculature itself. One area of research that shows promise in this context is the use of the anti-PSMA antibody J591.

**PSMA** is the most well established prostate-restricted, cell-surface antigen, expressed on both benign and metastatic prostatic tissue. J591 is a de-immunized monoclonal IgG1 antibody that targets the extracellular domain of PSMA. As noted by Sato et al, several trials using radiolabeled J591 have shown excellent targeting to known sites of prostate cancer, and phase I trials of radiolabeled J591 in metastatic androgen-independent prostate cancer have been published. A phase 2 trial of 177Lu-J591 is completing accrual, and trials assessing the utility of anti-PSMA-directed radioimmunotherapy in the biochemically relapsed setting and in combination with cytotoxic chemotherapy are in development. In addition to benign and malignant prostatic tissue, PSMA has been found to be expressed by the neovascular endothelium of many other solid tumor types but not by the vascular endothelium of normal tissue.[2,3] This pattern of expression makes PSMA not only an excellent target for the treatment of prostate cancer but also a potential candidate for antivascular treatment of other solid tumors. Furthermore, two independent phase I trials demonstrated the specific targeting of indium-111 labeled J591 to the neovasculature of solid tumors including cancers of the kidney, bladder, lung, breast, colorectum, pancreas, and melanoma.[4,5] These studies confirm the ability of J591 to selectively and specifically target therapy to the vasculature of metastatic cancers. Phase II trials testing the efficacy of radioimmunotherapy against solid tumor vasculature using anti-PSMA-directed therapy are in development.

**Conclusions**

The initial success of anti-VEGF antibodies and multitargeted tyrosine kinase inhibitors in the treatment of metastatic solid tumors has established proof of principle and encouraged the development of many new treatment modalities focused on the tumor vasculature. However, as is frequent in science, new discoveries lead to new questions. While we refine our current treatments and better define their role, a number of new targeted therapies are cresting the horizon. One such target is PSMA, which has antitumor activity in advanced prostate cancer and has potential in other malignancies. This specificity makes it an excellent candidate for the second generation of antivascular treatments, allowing for potentially more aggressive administration of cytotoxic agents. That said, we must recognize that the success seen with prior antiangiogenic treatments, while
exciting, was modest relative to their cost, was tempered initially by significant side effects, and did not lead to cure or complete replacement of traditional cytotoxic chemotherapy. As we move forward with more specific or nonspecific targeted therapies, it will be important to be vigilant for further unexpected side effects and to continually refine the treatments available to us. It is our hope that the new vascular-specific targets such as PSMA will continue to advance the successes and improvement in survival observed with the first generation of antiangiogenesis treatments.

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Disclosures: Dr. Arnason has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article. Dr. Tagawa is a member of the speakers bureau for Sanofi-Aventis and Pfizer. Dr. Bander is a consultant for BZL Biologics, Inc.

References:


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