

Advances in Drug Development

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Current Developments in Oncology Drug Research

Current Overview of Angiogenesis Inhibitors

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What is angiogenesis?

Angiogenesis is the process by which tumors or growing tissues establish a new blood supply. In order for tissues to grow, they need a blood supply for delivery of nutrients and oxygen. This requires the in-growth of new blood vessels.

When did the field of angiogenesis inhibition as anticancer therapy begin?

The field of angiogenesis inhibition really began by hypotheses raised by Dr. Judah Folkman of the Boston Children's Hospital, where he continues to do insightful research. Over the years, a number of pro- and antiangiogenic factors have been discovered. Initial attempts to inhibit the activity of the proangiogenic factors were somewhat disappointing in clinical trials. In animal models, numerous investigators have been able to inhibit the growth of tumors with the use of antiangiogenic agents. Yet when these studies were taken to the clinic, success was limited, until a very important study that was presented at the 2003 annual meeting of the American Society of Clinical Oncology (ASCO).

What are the different approaches to inhibiting angiogenesis?

The current approaches to inhibiting angiogenesis should be separated into 2 categories. The mainstay of antiangiogenic therapy research is the attempt to inhibit the effects of vascular endothelial growth factor (VEGF), probably the most potent angiogenic factor. In addition to its angiogenic properties, VEGF has a number of other important characteristics, including the induction of vessel permeability. A number of other proangiogenic factors, such as basic fibroblast growth factor, which was the first angiogenic factor identified, as well as interleukin-8 and a number of other factors, have also been targeted. Vascular targeting agents are another strategy for targeting VEGF.

The second category includes agents typically intended to target tumor endothelial cells. Some of these agents include integrin antagonists, endostatin, angiostatin, thrombospondin, and other endogenous or synthetic molecules. Although none of these agents that have been studied in clinical trials have been shown to benefit patients significantly, further trials are underway that will hopefully yield promising results.

What are the different strategies to targeting VEGF?

There are a number of different strategies to inhibit the activity of VEGF currently being studied. The most successful strategy to date has been the use of a neutralizing antibody that essentially soaks up VEGF and prevents it from binding to its receptors on endothelial cells. This is the mechanism of bevacizumab (Avastin, Genentech), the only antiangiogenic agent that has been approved by the US Food and Drug Administration (FDA). Other attempts to block VEGF activity include VEGF Trap (Regeneron/Aventis), a hybrid of VEGF receptors 1 and 2 designed to absorb VEGF and prevent it from binding to its receptor. IMC-1C11 (ImClone) is an antibody that targets VEGF receptor 2 and prevents binding of the ligand to the receptor. The largest class of molecules to inhibit VEGF activity is the tyrosine kinase inhibitors (TKIs), which inhibit not only VEGF receptors but also other tyrosine kinases as well. Several of these agents are in various stages of clinical trials, and at the 2004 ASCO meeting there were a number of interesting presentations in which the use of TKIs to VEGF receptors appeared to provide some benefit to patients with metastatic renal cell carcinoma. The majority of the data with the use of VEGF inhibitors have been in colon carcinoma.

What are vascular targeting agents?

The endothelial cells of the tumor vasculature are distinct from the endothelial cells in quiescent normal vasculature. The vascular targeting agents are thought to attack only the tumor vasculature. These agents lead to thrombosis of the tumor blood vessels, which in turn should lead to downstream tumor cell apoptosis. A number of these agents have been studied in phase I clinical trials moving to phase II, but they have not yet proven to be as effective as we had hoped. Similar to the anti-VEGF agents, the next step in the development of these agents may be their use in combination with standard chemotherapy or radiation therapy.

Could you describe the study presented at the 2003 ASCO meeting mentioned above?

At the 2003 ASCO meeting, Dr. Herb Hurwitz of Duke University presented data on behalf of his co-investigators

(and patients with metastatic colorectal cancer) demonstrating that the addition of bevacizumab (neutralizing anti-VEGF antibody) to the standard chemotherapy regimen at that time, irinotecan (Camptosar, Pfizer) plus 5-fluorouracil (5-FU) and leucovorin (LV) (IFL), led to improvements in median survival and response rates compared to patients receiving IFL alone. This was a large, prospective, randomized phase III trial with over 400 patients per arm, and was the first study to demonstrate a clinical benefit from the use of antiangiogenic therapy. This study was subsequently published in the *New England Journal of Medicine* in 2004.

How do antiangiogenesis agents work in combination with chemotherapy?

It is counterintuitive that the addition of antiangiogenic therapy to chemotherapy would yield an improvement in response rates. Antiangiogenic therapy, if it blocks the blood supply to the tumor, should limit the exposure of the tumor to chemotherapy. However, in several studies, even in studies that did not meet their primary endpoints, such as a randomized trial in breast carcinoma, the addition of bevacizumab to standard chemotherapy improved the response rate by approximately 10%. Antiangiogenic therapy appears to improve the effects of chemotherapy despite that this effect is counterintuitive.

This finding has led several investigators, including Dr. Rakesh Jain from Harvard University, and also myself, to hypothesize that VEGF therapies may work by another mechanism in addition to antiangiogenesis. One potential hypothesis initially raised by Dr. Jain is that the tumor microvasculature is very inefficient, and that anti-VEGF therapy can eliminate much of the inefficient vasculature, leaving behind only a very efficient vascular network that closely mimics the normal vasculature. Even though there may be more blood vessels in a tumor, those blood vessels are not necessarily functional, and in fact, may have turbulence of flow, or even no flow at all. Interestingly, in computed tomography scans of patients with liver metastasis, the liver enhances, but the liver metastasis appears to be relatively hypovascular compared to the surrounding vascular liver. Anti-VEGF therapy may “prune off” some of these inefficient blood vessels, providing for a more efficient vascular network, which is better for the delivery of chemotherapy.

A second hypothesis is that anti-VEGF therapy may work by lowering interstitial pressure. VEGF was initially termed vascular permeability factor (VPF) by Dr. Harold Dvorak at Beth Israel Deaconess Hospital in the late 1970s because VPF has the ability to induce permeability that is 50,000-fold higher than that of histamine. High vascular permeability leads to an increase in tumor interstitial pressure. Dr. Jain conducted a study in which he measured the interstitial pressure in tumors in both animal models and humans. In this study, it was found that the interstitial pressure in tumors may be 15–20 mm Hg, whereas in normal tissues interstitial pressure is 0–1 mm Hg. Blood will take the path of least resistance, which in this case would be the normal tissue. Therefore, decreasing tumor interstitial pressure would

improve blood flow to a tumor. By eliminating the permeability of VEGF or VPF, it is possible to decrease interstitial pressure and perhaps improve flow to a tumor.

Have any studies been done to test these hypotheses?

These hypotheses are supported by preclinical and now clinical studies. In preclinical studies, a decrease in tumor interstitial pressure was observed in tumor-bearing mice treated with anti-VEGF therapy. Other studies have demonstrated that pretreatment of mice with anti-VEGF therapy can lead to an increase in uptake of chemotherapeutic agents, and an increase in oxygen tension within the tumor, which signifies perhaps an increase in tumor blood flow. Some preclinical imaging studies also support these observations.

A very interesting study by Dr. Chris Willett, from the Massachusetts General Hospital, and Dr. Jain was published in *Nature Medicine* in January 2004. In this study, patients with locally advanced rectal cancer were given bevacizumab, and several measurements, including interstitial pressure in tumors, were taken before and after therapy. Following bevacizumab administration, patients received therapy with bevacizumab, 5-FU and radiation therapy, and subsequently underwent surgery. By taking measurements before and after anti-VEGF therapy, the investigators were able to evaluate the effects of anti-VEGF therapy alone on tumor interstitial pressure. This pressure decreased in the tumors of all 4 patients who could be measured both before and after therapy, suggesting that anti-VEGF therapy can indeed decrease tumor interstitial pressure.

Thus it seems that anti-VEGF therapy has multiple effects on the tumor vasculature. It may indeed inhibit angiogenesis, but more importantly it appears to augment the effects of chemotherapy.

Are other studies ongoing that are evaluating combinations of anti-VEGF agents with chemotherapy?

There are a number of studies about to be reported that will further define the role of this combination. One such study, CONFIRM 1 (Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases First-line), is evaluating oxaliplatin plus 5-FU/LV (FOLFOX) chemotherapy, the current standard chemotherapy regimen, plus or minus PTK787 (Novartis and Schering AG), a TKI to VEGF family members and platelet-derived growth factor receptor.

There are also a number of ongoing trials to determine if the addition of bevacizumab to FOLFOX is of greater benefit than FOLFOX alone. These include ongoing studies by the Southwest Oncology Group as well as a study in Europe sponsored by Roche.

Have any prognostic factors been identified that would indicate a patient likely to benefit from anti-VEGF therapy?

At the present time, there are no known predictive markers for the efficacy of anti-VEGF therapy, and this is a field where a great deal of investigation is needed. Although it is

intuitive that patients with high VEGF levels within tumors would respond better than patients with lower VEGF levels in tumors, pathologic evaluations from anti-VEGF therapy clinical trials have not shown this to be the case. It may be that the combination of anti-VEGF agents with chemotherapeutic agents complicates these types of evaluations. It is very important for us to recognize that when we speak about antiangiogenic therapy, at least in colon cancer, this refers not to single-agent antiangiogenic therapy, but to antiangiogenic therapy as a modifier of current chemotherapy regimens.

Have any studies of single-agent therapy with VEGF inhibitors shown promise?

Yes, in renal cell carcinoma. There have been a number of very interesting trials utilizing a variety of VEGF inhibitors as single agents. In the early stages of these trials, there have been responses in metastatic renal cell carcinoma patients treated with single-agent anti-VEGF therapy, even in a refractory setting.

Why does single-agent anti-VEGF therapy appear to be effective in renal cell carcinoma?

Renal cell carcinoma appears to be a predominantly VEGF-driven disease. Renal cell cancer mostly develops from loss of function of the von Hippel Lindau gene, which leads to overactivity of a transcription factor, hypoxia-inducible factor 1 (HIF-1). This loss of function leads to increased transcription of VEGF. The predominance of VEGF in the development of renal cell tumors is probably the reason why single-agent therapy with an anti-VEGF agent seems to be effective. In contrast, in other cancers, there appear to be multiple factors that may drive angiogenesis. Although VEGF may be the predominant angiogenic factor, there is likely to be redundancy in the system. It is important to gain a better understanding of the other effects of anti-VEGF therapy, so that we can determine whether this approach is modifying, rather than knocking out, the tumor vasculature.

Do patients become resistant to VEGF inhibitors, and how should such patients be treated?

It is difficult to determine at this point if patients become resistant to anti-VEGF therapy, to chemotherapy, or to the combination. Some investigators theorize that patients who progress on combination therapy should continue on the anti-VEGF therapy, but with a different chemotherapy regimen. If anti-VEGF therapy improves drug delivery to the tumor, and tumors might become resistant to the chemotherapy being delivered, then patients might benefit from a change in the chemotherapy regimen while maintaining the advantage of improved drug delivery with anti-VEGF therapy. This approach is still theoretical at the present time.

In the study by Hurwitz et al discussed earlier, patients who progressed on IFL plus bevacizumab were allowed to receive second-line therapy that included bevacizumab plus another chemotherapy regimen. In those patients who initially received IFL plus bevacizumab and then received an oxaliplatin-based regimen plus bevacizumab, the median survival was extended to approximately 25 months. In contrast, the median survival

with IFL alone is approximately 15 months, and 22 months with second-line oxaliplatin-based therapy. These findings are in keeping with studies by Tournigand and Grothey, in which survival correlated with the number of drugs received.

Of course, the inherent bias in this finding is that the patients who have the best performance status are going to receive more drugs than those who have a lesser performance status. However, it is promising that some patients can achieve a median survival of at least 25 months when more chemotherapeutic agents as well as anti-VEGF therapy can be administered.

With so many potential combinations, what is the best way to evaluate antiangiogenesis agents plus chemotherapy in clinical trials?

We are still not exactly sure of how to develop these agents in clinical trials. Safety and toxicity must be determined in phase I trials with dose escalation. However, the overall paradigm will most likely be to add the antiangiogenic agent to the standard chemotherapy of the day.

This approach has some inherent challenges, since standard chemotherapy regimens change. For example, identifying the best combination for colorectal cancer has been difficult, since the standard therapeutic regimen has changed rapidly over time. This change is very good for patients since it means we are improving our therapies. However, by the time a randomized trial of chemotherapy plus or minus antiangiogenic therapy is completed, the standard chemotherapy regimen has already changed. This situation has occurred twice in the last 4 or 5 years.

On the other hand, a lack of a standard regimen also presents challenges. In contrast to colorectal cancer, in renal cell carcinoma, there is no standard chemotherapy regimen. Here, although a number of randomized trials are ongoing, it is difficult to determine what the standard of care should be.

What side effects are associated with anti-VEGF therapy?

Hypertension has been a consistent side effect across all trials with all anti-VEGF agents with all diseases. This side effect is easily controlled by either adding an antihypertensive agent or increasing the dose of an ongoing antihypertensive agent. The occurrence of hypertension is probably due to the fact that VEGF induces nitric oxide and prostacyclins, which lead to vasodilation. Inhibiting VEGF activity decreases the vasodilatory effect of VEGF, leading to vasoconstriction.

In early trials, there was some concern about proteinuria. This toxicity has been less of a concern in more recent trials, although it should still be followed with patients on anti-VEGF therapy. Bowel perforation has also been observed, although there does not appear to be any pattern to its occurrence. In the study published by Hurwitz et al in the *New England Journal of Medicine*, 6 bowel perforations were observed in the IFL plus bevacizumab group, versus only 1 occurrence in the IFL plus placebo group. However, this

adverse event did not appear to occur at sites of tumor or within intraperitoneal carcinomatosis, or in any other discernible pattern. The package insert for bevacizumab warns of the possibility of bowel perforations.

Special care must be taken with patients undergoing surgery while on anti-VEGF therapy. Antibodies typically have a long half-life, and the average half-life of bevacizumab is approximately 20 days. Therefore, if a patient is going to have elective surgery, it is suggested that this take place at least 2 half-lives, or at least 40 days, after bevacizumab therapy. VEGF is very important in wound healing following surgery. An earlier report from Gordon et al noted that as little as .3 mg/kg of bevacizumab could remove all circulating VEGF from the blood. Today, this agent is used at a dose of 5–10 mg/kg, so there is very little free circulating VEGF in patients who receive this agent. For patients who must undergo emergency surgery, the surgeon must be aware that the patient is on bevacizumab and should take extra precautions to prevent anastomotic leakage and other potentially hazardous situations.

Suggested Reading

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