Novel Antiangiogenic Therapies for Renal Cell Cancer

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ABSTRACT
Renal cell cancer remains a disease for which highly effective therapy for the majority of patients with metastatic disease is lacking. The biology of clear cell carcinomas and their association with mutations of the von Hippel-Lindau gene and its resultant increased expression of vascular endothelial growth factor (VEGF) make angiogenesis a potentially pathophysiological mechanism for tumor development. As a result, the use of antiangiogenic therapy is an intriguing concept for the treatment of renal cell cancer. Various agents, aside from the inhibitors of VEGF, have been studied, including thalidomide, low-dose interferon, and novel antiangiogenic agents such as the thrombospondin-1 mimetics. Use of these agents has been associated with some degree of objective response or prolonged stabilization of disease, and their true value needs to be assessed in ongoing prospective studies. Combinations of antiangiogenic agents either with other similarly acting drugs or as a component of a “cocktail” with other noncytotoxic therapies should be explored in this patient population.

BACKGROUND AND INTRODUCTION
The use of antiangiogenic therapy for the treatment and management of metastatic renal cell cancer (RCC) is specific for patients with the clear cell histologic features. On the basis of the frequency of mutations in the von Hippel-Lindau (vHL) gene as previously described, the up-regulation of vascular endothelial growth factor (VEGF) makes clear cell RCC an ideal target for VEGF inhibitors.

Angiogenesis is a process that has a number of different components that can be targeted in a variety of ways. In a general sense, optimization of antiangiogenic therapy will likely require a combination of these different approaches. Table 1 provides an overview of the cellular and biological processes involved in angiogenesis and also serves as an outline for the targeting of this process. Agents that are specific for endothelial cells may inhibit their proliferative and migratory capacity as is seen with the VEGF inhibitors. Withdrawal of VEGF at a critical point in the life span of an endothelial cell will result in apoptosis and cell death. Alternatively, the use of agents that inhibit basement membrane degradation, typically by blocking the family of enzymes known as the matrix metalloproteases (MMPs), can inhibit migration of endothelial cells. Finally, maturation of new tubules and the development and maturation of new vessels remain the last critical phase that may be considered in the therapeutic process.

A number of agents have been studied in the treatment of metastatic RCC, with various results. This article will review the non–VEGF-directed therapies and antiangiogenic strategies for their clinical use and benefit.

THALIDOMIDE
Thalidomide is a nonspecific antiangiogenic agent that has activity at a number of different levels. Its antiangiogenic activity was first demonstrated by D’Amato et al. (1) Thalidomide inhibits angiogenesis via a variety of mechanisms. Fujita et al. (2) have demonstrated that thalidomide and its related immunomodulatory drugs have the ability to inhibit cyclooxygenase (COX)-2 translation and thereby down-regulate COX-2 production, although not its enzymatic activity. In addition, thalidomide can decrease VEGF-induced activation of endothelial cells, can reduce expression of tumor necrosis factor α, and is immunomodulatory.

Thalidomide was first studied in RCC as part of an initial trial by Eisen et al. (3, 4) in which a low dose of 100 mg/d was administered orally to patients with cancer. Objective responses were seen, suggesting that this agent may have antitumor activity. Toxic effects of thalidomide include sedation, constipation, peripheral neuropathy, and rash. These effects tend to be dose related and complicate dose escalation to achieve the possible dose-related anticancer activity of thalidomide. Subsequently, there have been a series of phase 2 trials, with various doses of thalidomide ranging from 100 to 1,200 mg/d (5–8). An overview of these phase 2 trials is provided in Table 2. Objective anticancer activity is seen in a few patients, with response rates ranging from 0 to 10%. Of interest, however, is the reproducible ~30% progression-free survival at 6 months in what is typically a group of relapsed and refractory cancer patients. Unfortunately, the toxic effects of thalidomide typically preclude the ability to escalate doses to the highest doses, and most patients tolerate long-term dosing in the range of 400 mg/d, which has eventually become the de facto recommended maximum dose for the treatment of patients with cancer.

The combination of thalidomide with other anticancer strategies has been explored in patients with metastatic RCC. Desai et al. (9) combined thalidomide with a combination of 5-fluorouracil and gemcitabine. The chemotherapy regimen was previously studied alone in patients with advanced RCC and demonstrated a 16% overall response rate with a reasonable safety profile. When thalidomide was added to this regimen, an increased incidence of the thromboembolic phenomenon was
seen, including five deep vein thromboses, three pulmonary emboli, and one fatal cardiac arrest, for a venous thromboembolic event rate of 43%. No complete responses were seen, and there were only two partial responses, for an overall response rate of 10%. Two studies have been conducted with the combination of thalidomide and interleukin 2 (IL-2), with acceptable toxic effects and varied degrees of response. Amato et al. (10) conducted a phase 1/2 trial of this combination, and their results indicated objective responses in 15 of 36 patients. In contrast, the phase 2 trial conducted by Olencki et al. (11) produced considerably less antitumor activity, indicating that controlled studies need to be done to better assess this combination.

The combination of interferon and thalidomide has received a great degree of attention. A study assessing the combination of standard thrice-weekly interferon α with thalidomide produced unacceptable neurotoxic effects, including seizures, neuropathy, and stroke-like symptoms (12). The trial was terminated early because of these toxic effects, and no determination of the antitumor activity could be assessed. In contrast to standard-dose interferon α, lower doses of this agent have been associated independently with antiangiogenic activity in children with hemangioma (13). As a result, the combination of low-dose interferon with thalidomide has been explored as a means of providing combination therapy. Hernberg et al. (14) performed a phase 2 trial of low-dose interferon (0.9–1.2 MU subcutaneously thrice daily) with escalating doses of thalidomide. This combination was well tolerated, and a response rate of 20% was seen in 30 patients. A randomized phase 3 trial of low-dose interferon alone or in combination with thalidomide has been completed, and the preliminary results fail to demonstrate an overall survival advantage for the addition of thalidomide to interferon (15).

Newer analogs based on the thalidomide molecule with better safety profiles characterized by no sedation or constipation are currently being studied. Clinical trials in RCC have been initiated, and the enhanced biological activity of these agents holds the potential to improve on the antitumor activity that has been seen with thalidomide.

**THROMBOSPONDIN-1 MIMETIC**

Among the naturally occurring antiangiogenic proteins, thrombospondin-1 (TSP-1) is recognized as being critically important. A balance exists between proangiogenic factors, such as VEGF or basic fibroblast growth factor (bFGF), and the natural antiangiogenic factors, such as TSP-1 and interferon α among others. TSP-1 is a large, multifunctional protein that is transcriptionally activated by the tumor suppressor gene product p53 (16). TSP-1 binds to CD36 on the surface of endothelial cells and inhibits their ability to migrate while inducing apoptosis in these cells (17). As a result, it has been applied clinically as a potentially novel antiangiogenic agent. Unfortunately, the TSP-1 molecule is exceedingly large, preventing its application as a therapeutic agent. As a result, several TSP-1 mimetics have been developed based on the identification of the NH₂-terminal portion of the peptide being responsible for the antiangiogenic activity. Initial studies with ABT-526 in dogs with naturally occurring tumors which had progressed after initial standard therapy revealed objective responses in 8 of 56 evaluable dogs (18). These responses occurred across a breadth of diseases, including both solid tumors and lymphomas. As a result of the preclinical activity for this class of agents and the insights from the veterinary study, two phase I trials with another analog, ABT-510 were conducted (19, 20). The doses studied ranged from 10 to 260 mg administered subcutaneously without dose-limiting toxic effects. Stabilization of disease was seen in a number of patients with both soft tissue sarcoma and RCC. At least one patient experienced a delayed response after initially demonstrating progressive disease. As a result of the results of the phase 1 trials, a randomized phase 2 trial that assessed doses of 10 versus 100 mg as twice-daily subcutaneous injections is being conducted in patients with metastatic RCC.

**TNP-470**

TNP-470 represents one of the first-generation antiangiogenic agents. It acts by inhibiting endothelial cell proliferation in the setting of activation by bFGF. Having demonstrated some degree of activity in phase 1 trials, a phase 2 study of this agent was made in patients with relapsed and refractory RCC (21). On a thrice-weekly bolus dosing schedule, patients with refractory disease were treated at a dose of 60 mg/m² daily. Thirty-three patients were enrolled in the trial, with a median of two prior regimens. Although TNP-470 was generally well tolerated, little antitumor activity was seen. Six patients remained in the study for at least 6 months, but only one partial response of short duration was observed.

**CARBOXYAMIDOTRIAZOLE**

A variety of additional agents have been proposed to have antiangiogenic activity through less well-described mechanisms of action and have been studied in patients with RCC. Carboxyamidotriazol is an agent that inhibits calcium flux and is believed to thereby inhibit endothelial cell motility. A single-agent phase 2 trial made by the Eastern Cooperative Oncology Group demonstrated only one partial response and limited ability of the agent to stabilize disease (22). The median time to
progression was 3.2 months, and only 25% of the patients were progression free at the 6-month point. Median survival in this previously treated patient population was 11 months, suggesting either potential activity or, more likely, potential selection bias. A subsequent study that used the randomized discontinuation trial design was made by Cancer and Leukemia Group B. This design depends on the induction of stabilization by the investigational agent to provide patients for the randomization. Unfortunately, the randomization rate of 18% was lower than expected in the first 374 patients accrued, indicating that the agent was not having the desired disease stabilization effect. In addition, for the first 49 patients who completed the randomization, no significant difference was seen in the maintenance of the stability. As a result, the likelihood of detecting a statistically significant benefit was less than 9% if accrual continued, and, hence, the trial was stopped (23).

MATRIX METALLOPROTEASES

The MMP inhibitors were among the first antiangiogenic agents studied in cancer patients. They received extensive assessment in a broad range of malignant diseases because of their ability to inhibit MMP-2 and MMP-9, thought to be important for an early stage of angiogenesis. There were no specific notations of responses or even prolonged stabilization in patients with metastatic RCC. No large trials have been done in RCC with prinomastat or marimastat; however, these agents both failed to produce clinically meaningful results in randomized phase 3 trials in a number of more common malignant diseases. As noted above, single-agent antitumor activity was not generally seen for this class of agents. One agent that has both MMP inhibitory activity and VEGF inhibitory activity is AE-941 (Neovastat). In patients with RCC, this agent was initially studied in a randomized trial that compared two doses of therapy (60 versus 240 mL) in 144 patients with refractory solid tumors, of whom 22 had refractory RCC (24). Although the statistical value of such a subgroup comparison is questionable, there appeared to be a dose-response relationship, with the 14 patients receiving the higher dose having a median survival of 16.3 months compared with the 8 patients taking the lower dose, whose median survival was 7.1 months. The results of this two-arm study led to a randomized, placebo-controlled phase 3 trial in patients with immunotherapy-refractory RCC (25). In the latter trial, 302 patients were enrolled and randomized between AE-941 at a dose of 120 mL and placebo administered orally twice daily. No difference in survival was seen for the overall population, which indicated that this drug, as a single agent, had limited activity in patients with refractory RCC. Other MMP inhibitors, such as BMS-275291 and COL-3, have also been studied in cancer patients, but no definable activity in RCC has been noted.

SUMMARY AND CONCLUSION

The use of antiangiogenic agents is supported by the emerging data for VEGF and receptor tyrosine kinase inhibitors. Response rates of ~10 to 15%, with a larger number of patients experiencing stable disease, indicate that this family of therapies may need to be combined either with each other or with other effective therapies. Among the drugs actively being combined, the greatest experience is with thalidomide. Unfortunately, no clear evidence of enhanced activity exists for combinations of interferon, IL-2, or other therapies with thalidomide. It is hoped that additional studies with more highly active analogs will provide a greater degree of insight into proper combinations. Recent data that indicate that the vhl gene mutation may regulate factors such as the angiopoietins and their receptor Tie2 are further evidence of the importance of angiogenesis in RCC and the potential for the use of this class of agents in patients with metastatic disease (26). Markers for biological activity in RCC do not reliably exist to ensure accurate assessment of antitumor activity in these studies. In addition, the commonly recognized indolent behavior of some patients’ tumors reinforces the need for controlled trials in this disease. The example of the randomized discontinuation trial design used for the carboxamidotriazole trial and recently for BAY 43-9006 suggests that this design may be aptly suited for the patient population of metastatic RCC.

OPEN DISCUSSION

Dr. Michael Atkins: What is the appropriate place for antiangiogenic therapy in the treatment of patients with renal cancer? Should we be testing these agents first line, and what should we be telling patients who come in and ask for bevacizumab or another agent, if they’ve had no other treatment for kidney cancer?

Dr. Michael Gordon: Most of the patients we put on the phase 2 trial are patients who were ineligible for high-dose IL-2; our oldest patient is 79. One of the things that might be very valuable is having a consensus about what the standard response criteria or response evaluation criteria should be, because we talked about at least three different response criteria. Maybe we should reconcile that so that people who are doing the studies can make sure that we at least have data that are comparable. The big issue is going to be incorporating biology. We have to figure out novel ways of asking whether we are hitting targets so that we can intelligently work with combinations.

Dr. Allan Lipton: Do you think that with these agents we should look for the appearance of new lesions, which would go with failure?

Dr. Walter Stadler: Our standards for looking at response are fine, but they’re arbitrary. It is a number that allows us to all speak the same language. I don’t think you have to redefine that. The part that is a bit different is that we are seeing what we really think is disease stabilization. Unfortunately, because of the variable natural history of renal cancer, in an uncontrolled study, the stable disease rate, no matter how you define it, is essentially meaningless. The only way that you can then attach any kind of meaning to the 10% or 20% responses is through some kind of controlled trial. A stable disease rate in a single-arm study is not particularly meaningful.

Dr. Robert Flanigan: Perhaps then, the end point becomes survival, in that situation. I don’t know how you would quantitate anything else. You have no idea whether the responses mean anything.

Dr. Stadler: It depends on what you’re doing. In a controlled phase 2 study, you can have a nonsurvival end point and
still can define drug activity. You do not define whether the drug has benefited the patient, but it will allow you to screen the drug for antitumor activity. For example, in Dr. Yang’s study, he defined the drug as having activity; it is slowing disease progression, and we know this because it is a controlled study. Although the study has not yet proven that the drug actually benefits patients in terms of survival and quality of life, it did establish that the drug has activity. We will need to do phase 3 studies to demonstrate whether there is improvement in survival.

Dr. Daniel George: I think the field is changing. With the number of agents that are going to be available and the number of studies that are going to be out there, placebo-controlled studies are going to be very difficult to complete. I think we need some way of judging these therapies in a randomized setting that is not necessarily placebo controlled.

Dr. Stadler: I said controlled setting; I didn’t say placebo controlled. I think if you are going to look at nontraditional end points, you have to have a control. Bill Kaelin would never do a study in the laboratory in which he would give a bunch of mice a drug and didn’t control it, yet we do these kinds of things all of the time in our clinical trials.

Dr. Robert Motzer: The standard ways that we have of assessing outcomes are response, time to progression, or survival. In effect, what we are seeing, probably, with stable disease is some prolongation of survival time, so that is an end point we can look for in these drugs. With regard to the criteria, I think it is RECIST (response evaluation criteria in solid tumors involving multiple measurements of a single diameter of tumor thickness) across the board in oncology. So, coming up with a different response, a different means of assessing the time to progression, is difficult.

Dr. Gordon: I didn’t mean a different means. I just meant let’s all use RECIST and make sure that subsequent studies use that for defining end points as well.

Dr. Flanigan: In Southwest Oncology Group (SWOG), we have been discouraged by our statisticians from doing randomized phase 2 trials. If you do a smaller phase 3 trial, looking for a significant survival advantage as an end point, you are going to be missing very little. I don’t understand the downside of using that kind of approach.

Dr. James Yang: I think that trying to decide on consistent criteria for any of these things doesn’t make sense. We can use conventional, or at least common, end points, but they should be tailored to the biology we expect.

Dr. Robert Figlin: The conundrum we’re in is, in part, because the molecules that we use still have modest activity. For those of us who have been doing kidney cancer for the past couple of decades, this discussion is not new. We ultimately have to identify mechanisms and biology that do something more than the modest things we are currently seeing. Our goal in cancer therapy should be cure.

Dr. Flanigan: It sounds like we have no problems with the number of agents that could be tested, but what needs to be established for all of the groups is common criteria about how the drug efficacy is going to be judged.

Dr. Stadler: It depends completely on whether you are trying to determine activity in phase 2 trial or trying to determine benefit. There is a big difference. If you have a new drug, you want to know if it is even worth studying in a large phase 3 trial with survival as the end point. A study with survival as the end point is going to be a big, expensive study. We cannot take every single one of the drugs that are potentially interesting and do a 700-patient study. You have to be able to select the ones that are most useful.

Dr. Yang: I think we all agree that combinations are necessary. But if I want to combine two agents and I haven’t seen their biological effect on patients independently, there are too many permutations to get through that trial. Therefore, it is not at all clear to me whether the agents alone will produce survival benefits; however, there remains a value in gathering information about their biological activity.

Dr. Flanigan: I’m not saying you should try to obtain biological correlates. But at some point along the road, the biological correlates in and of themselves don’t translate into the need to test the drug in combination with other drugs, unless there is some degree of efficacy shown from a clinical perspective.

Dr. Figlin: I want us to remember that we need to be on a different path in taking targeted therapy forward than we were 30 years ago, when we were just combining targeted cytotoxic agents because they didn’t have overlapping toxicity. I still think we need to understand biology.

Dr. William Kaelin: The only reason I can see not to do controlled, small phase 2 studies is that you run the risk of missing small effects that would have otherwise revealed themselves in massive, expensive studies. If we decide as a community that we are not interested in effects that are so small, it makes sense to do Dr. Yang’s type of study. Hopefully, we’ll have some rational hypotheses from preclinical studies that won’t require 700-patient trials.

Dr. Atkins: The only way you can show small differences is with trials; the only way you can be definitive is to have a lot of patients. We have so many agents that we may want to set the bar a little higher and look for bigger differences. One of the problems is that with all of the studies out there, it is going to be hard to see survival differences, because patients on placebo in one trial are going to find their way to another drug that may work similarly and it may compromise the survival end point. We are going to have to figure out ways of using intermediate end points to guide our drug development and aid in rationally choosing appropriate combination regimens.

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