Bevacizumab for Patients with Metastatic Renal Cancer: An Update

James C. Yang
Surgery Branch, National Cancer Institute, Bethesda, Maryland

ABSTRACT

Most clear cell renal cell cancer (RCC) is caused by biallelic loss of the von Hippel-Lindau gene. One consequence of this loss is up-regulation of vascular endothelial growth factor via a pathway involving accumulation of hypoxia inducible factor. Vascular endothelial growth factor, a potent angiogenic factor, is secreted by many human cancers, but clear cell RCC as a group produces particularly high levels and has a highly vascular histologic appearance. In a randomized, placebo-controlled, double-blind trial, we tested the use of a neutralizing antibody to vascular endothelial growth factor, bevacizumab, in patients with metastatic RCC. At 3 or 10 mg/kg every 2 weeks, toxic effects were minimal, with hypertension and proteinuria the most substantial events. There were four partial responses (10% response rate) and a highly substantial prolongation of time to tumor progression in patients who received the higher dose of bevacizumab. With a crossover design and very sensitive criteria for disease progression, no difference in survival was shown. Four patients have been undergoing long-term bevacizumab therapy without tumor progression for 3 to 5 years. Three have substantial proteinuria but retain normal renal function. A small pilot trial combining bevacizumab and thalidomide showed no unexpected toxic effects. Future trials should consider combination therapies and strategies in which patients are treated through initial disease progression with antiangiogenic agents such as bevacizumab.

Most clear cell renal cell cancer (RCC) is caused by biallelic loss of the von Hippel-Lindau tumor suppressor gene (1). One consequence of this loss is up-regulation of vascular endothelial growth factor (VEGF) via a pathway involving accumulation of hypoxia inducible factor (2). VEGF, a potent angiogenic factor, is secreted by many human cancers, but clear cell RCCs as a group produce particularly high levels and have a highly vascular histologic appearance. For >50 years, investigators have hypothesized that inhibiting the ability of a growing tumor to generate needed vasculature could represent a therapeutic strategy for cancer (3). This hypothesis was validated, pursued, and popularized recently by Folkman (4) in murine models. VEGF has proven to be a central mediator of neovascularization and the angiogenic response to hypoxia. In applying these findings to patient treatment, Presta et al. (5) humanized the murine A.4.6.1 antibody to human VEGF, producing bevacizumab. The amino acid sequence of this monoclonal antibody is 93% of human (IgG framework) origin and 7% murine (from the complementarity-determining regions of A.4.6.1).

Gordon et al. (6) administered bevacizumab at 0.1 to 10 mg/kg in a phase 1 trial and saw infrequent toxic effects, with the most substantial being tumor bleeding in 3 of 25 patients. Because of the mechanistic link between VEGF overexpression and von Hippel-Lindau inactivation in clear cell RCC, we undertook a randomized, placebo-controlled, double-blind study of bevacizumab in patients with measurable metastatic clear cell RCC (7). The two bevacizumab doses selected were 3 mg/kg (predicted by pharmacokinetics to produce a serum level equal to the optimally effective level of A.4.6.1 in nude mice bearing human tumor (xenografts) and 10 mg/kg (the maximum dose in the phase 1 trial, although limiting toxicity was not reached). Beginning 1 week after a loading dose of 150% of the assigned dose, treatment was given by intravenous infusion every 2 weeks. The primary end points were time to tumor progression (by World Health Organization criteria) and response rate. Survival was a secondary end point, because crossover from placebo to 3 mg/kg of bevacizumab was allowed for patients progressing with placebo.

One hundred and sixteen patients of a planned 150 patients who were randomized (40 to placebo, 37 to low-dose bevacizumab, and 39 to high-dose bevacizumab) before terminating accrual in accordance with early stopping criteria for time to progression. Toxic effects were minimal, with hypertension and proteinuria (without reduction in renal function) the primary treatment-associated toxic effects. Assessments of patients taking bevacizumab showed no evidence of antivevacizumab antibody generation with treatment, and there was a consistent rise in plasma VEGF levels in patients taking both doses of bevacizumab but not in patients taking placebo. Although we cannot rule out reduced clearance of VEGF when it is bound to bevacizumab as the cause of this increase (the assay detects free and bound VEGF equally), an increase in VEGF levels has also been seen in patients in some phase 2 studies of small molecule inhibitors of the VEGF receptor, kinase domain receptor, suggesting a feedback loop activated by biologically effective blockade of VEGF. It would have been of major interest to perform molecular studies of patient tumors before treatment, attempting to identify predictors or correlates of stability on bevacizumab, but the inaccessibility of most renal metastases and concerns about wound healing after surgical procedures did not allow this. Another issue was the exclusion of patients with symptomatic bony metastases in weight-bearing sites. This
study included 11 patients with bone metastases (2, 3, and 6 patients assigned to high-dose bevacizumab, low-dose bevacizumab, and placebo, respectively), but some of these patients showed increased bone-related symptoms while taking bevacizumab despite no evident tumor growth. The effects of VEGF neutralization on bone remodeling rather than tumor growth could have confounded this observation; therefore, these patients were not enrolled subsequent to this observation. This was not thought to affect the overall conclusions of the study. There was no significant difference in the enrollment of patients with bone involvement between the arms, and reanalysis excluding all 11 of these patients resulted in no changes in the overall results. In this trial, there were four partial responses (10% response rate) and a highly substantial prolongation of time to tumor progression in patients receiving the higher dose of bevacizumab. There were no major responses to the 3 mg/kg dose, and the effect on time to progression was minimal and of borderline statistical significance. No difference in survival was shown.

A substantial number of patients taking bevacizumab showed evidence of mixed tumor responses. Because sensitive criteria for tumor progression were used (a 25% increase in the product of perpendicular diameters of any lesion; even a single lesion increasing in diameter by 12% could meet this criterion), protocol therapy was truncated in some patients who may have been experiencing a net benefit from bevacizumab. Data to support this conjecture, especially in those patients randomized to high-dose bevacizumab, are found when tumor burdens during treatment are examined (Fig. 1, data expressed as percentage of change from baseline of the sum of the products of perpendicular diameters of all measured lesions; ref. 8). This shows that most patients receiving 10 mg/kg of bevacizumab came off of protocol with less tumor than they started with, most as the result of mixed responses, where progression occurred only in a minority of their lesions. Even a subset of patients given 3 mg/kg of bevacizumab showed net tumor stability during the study, a feature rarely seen in patients receiving placebo. These findings strongly support the concept of continuing treatment despite limited tumor progression and the use of new, novel, and lenient criteria for stopping protocol therapy with overall survival as the end point.

The completed randomized study showed that the most likely effect of bevacizumab in patients with clear cell RCC was a slowing of disease progression rather than major tumor regression. Because this was likely to lead to long-term, prolonged therapy, it became important to understand the long-term efficacy and toxicity of bevacizumab. Four patients have been undergoing long-term bevacizumab therapy without tumor progression for 3 to 5 years. Two completed 2 years of therapy at 10 mg/kg without tumor progression (one partial response and one minor response) and then discontinued therapy as dictated by protocol. Both then relapsed to their baseline tumor burdens and began taking bevacizumab again under compassionate use circumstances. Both reattained their previous tumor regressions and have remained stable on treatment for an additional 3 to 3.5 years. Two other patients (one initially randomized to and treated with 3 mg/kg on protocol, and the other randomized to 10 mg/kg) remained stable while undergoing protocol therapy but then subsequently received 10 mg/kg under compassionate use circumstances. Both remained stable and continued to take bevacizumab for a total of >4 years. Three of these patients receiving prolonged bevacizumab therapy have substantial proteinuria (in some cases >= 3.5 g/day), but all retain normal renal function. Therefore, the toxic effects of long-term bevacizumab therapy seem limited and primarily consist of proteinuria, supporting the feasibility of treatment strategies that use this cyto-

![Fig. 1 Total measured tumor burdens (sum of products of perpendicular diameters) depicted as percentage of baseline burden for each patient with metastatic renal cancer during treatment with either placebo, 3 mg/kg of bevacizumab, or 10 mg/kg of bevacizumab (7, 8). Adapted from Elaraj et al. (8).](cancerrresearch.aacrjournals.org)
static agent in a prolonged fashion. In addition, the reattainment of responses in patients who relapse off of therapy and the prolonged disease stability of these patients who have now been treated in excess of 4 years indicate that tumor resistance or escape from single-agent VEGF blockade may not be inevitable.

Patients in this trial who were randomized to placebo and showed tumor progression were initially crossed over to low-dose bevacizumab monotherapy as given on one arm of the trial. Because of the redundant nature of the information generated, the shortage of bevacizumab at the time, and the need to explore new strategies in the use of antiangiogenic agents, it was proposed that patients who showed tumor growth in the placebo arm be offered crossover to a pilot trial of bevacizumab combined with another experimental antiangiogenic agent, thalidomide. Because the number of patients available for such a pilot study was small, intrapatient dose escalation was used to rapidly assess the toxicity and tolerance of adding thalidomide to 3 mg/kg of bevacizumab (8). Escalating thalidomide from 200 mg/day to a maximum of 800 mg/day along with biweekly bevacizumab showed only expected toxic effects and validated the theory that meaningful doses of thalidomide could be combined with 3 mg/kg of bevacizumab. The median dose of thalidomide reached after escalations of 100 mg/day every 2 weeks was 500 mg/day. Although efficacy assessments could not be made on the small sample in this trial, there were no major responses in 12 patients, and times to progression seemed similar to those seen with 3 mg/kg of bevacizumab alone.

It is likely that combination trials with bevacizumab will be needed in the future to enhance the activity seen with single-agent therapy. These combinations should target both parallel loci (VEGF and non-VEGF) and serial loci (multiple points “upstream” and “downstream” within the VEGF pathway) in angiogenesis pathways, because dose-limiting blockade of the VEGF pathway was not achieved in the randomized trial. In these combination trials, knowing the efficacy of each of the agents used will be critical to rapid progress. It is hopeless to combine multiple agents with unproven or unknown clinical efficacy, hypothesizing that they each are active (but ineffective as monotherapy) and that the simultaneous application of a multipronged attack on angiogenesis will cause major antitumor impact. Instead, small, single-agent, randomized, carefully controlled studies with clinical or biological end points should be used to identify a repertoire of active targeted agents that can then be combined in rational and predictable ways to more definitively push the tumor angiogenic switch to “off.”

OPEN DISCUSSION

Dr. Michael Gordon: On the patients who you crossed over to bevacizumab or bevacizumab-thalidomide, if you reverse and go backwards to their time on placebo, is there any sense of a change in the rate of their progression after they transitioned over to the bevacizumab-containing therapy?

Dr. James Yang: Very small numbers.

Dr. Michael Atkins: Can you connect the tumor size curves from the two studies?

Dr. Yang: Yes, you can, but we didn’t feel that was necessarily valid, because it is more or less second-line treatment, with placebo being first line. We don’t know anything from these crossover data about efficacy yet.

Dr. Atkins: Bob Motzer, you looked at a lot of second-line patients, which is what this group is. Do you think that the placebo arm is typical of the placebo arm that you looked at in terms of how fast their disease is growing?

Dr. Robert Motzer: The patients in our studies who have gone on second-line therapies with inactive drugs mostly progress by 2 months. It is dependent on the criteria you use to define disease progression. Although most of our studies, historically, have used the World Health Organization criteria as well.

Dr. Yang: That’s going to make a big difference, because the biggest discrepancy between RECIST (Response Evaluation Criteria in Solid Tumors) and World Health Organization is in the progression criteria. The other criteria usually match up pretty well.

Dr. Gordon: The studies that have been done comparing World Health Organization and RECIST show them to be pretty similar. Bob Motzer’s paper in Cancer is critically important, because probably over 80% of your patients had nephrectomy. Having primary tumors in place makes a huge difference in terms of being able to discern response or progression.

Dr. Motzer: We did a study where we had 50 patients with kidney cancer who were treated either with interferon or thalidomide, and we had two different radiologists assess their response and time to progression according to the two criteria. There was a difference with the RECIST criteria being a longer and probably a better marker of time to progression. But whether the kidney was in or not also made a difference, because you obviously got this big mass that adds to the baseline measurements and dilutes out the relatively small changes seen in the metastases.

Dr. Yang: Ninety percent of the people in this trial had their kidney tumor resected, and all of those parameters were matched very well between these groups. There were slightly more bone metastases in one group, but it was 6 versus 2, and eliminating them did not change the data at all.

Dr. Allan Lipton: Is there anything in the pattern of spread that might give you a clue as to whether this drug works better in one site than another?

Dr. Yang: No. The only other concern I had was the bone metastases issue, and, of course, because VEGF is critical in bone remodeling, that may have been its prominent effect rather than a cancer effect. For example, a patient with a persistent bone lesion, not changing at all, became very symptomatic, required radiation and had to come off trial, and yet had no soft tissue tumor growth. Situations like this led to confusion about progression status, so ultimately we stopped enrolling patients with bone metastases.

Dr. Gordon: We saw that as well on the phase 1 trial in two patients. One was a gentleman who predominantly had lung disease who had a minor response on either the 3 or 10 mg/kg dose level. He also had metastatic bone disease, which ultimately progressed despite his having a response in his lungs. He had to come off therapy to get radiation. The other patient was a woman with hepatic disease, who basically looked like she cavitated out her hepatic lesions, but then she eventually progressed in bone.
Dr. Yang: I saw the opposite pattern as well. It seems to be a lesion-to-lesion issue more than a site-specific issue for the patients.

Dr. Robert Flanagan: What was the timing of the nephrectomy of those patients?

Dr. Yang: Most of them had a remote nephrectomy before they had received interleukin-2.

Dr. Robert Figlin: Dr. Kaelin, when you induce HIF, how does HIF control the variety of VEGFs produced?

Dr. William Kaelin: There are certainly HIF-binding sites in the promoters for these genes, and HIF may also indirectly affect the stability of the mRNAs, but certainly for many of these HIF targets, there are bona fide binding sites in their promoters that HIF recognizes and then activates transcription.

Dr. Tim Eisen: Regarding toxicity, particularly in the combination study that you subsequently did, am I right that there was no thromboembolic problems?

Dr. Yang: The only pulmonary embolism that occurred on this trial was in a patient who received placebo.

Dr. Eisen: Is that true for the combination treatment as well?

Dr. Yang: Yes, but they are all small numbers. In the combination trial, neuropathy was the major reason for limiting the thalidomide. We didn’t see any augmentation of the neuropathy by dose, and the only other major toxicity was an episode of coma related to hypertension. However, hypertension is something that you see even with bevacizumab. It was a little unexpected and unpredictable in that the onset was often months into treatment and it came on very briskly without warning. I have my patients take a blood pressure cuff home, check their own pressure routinely, and call us for certain thresholds.

Dr. Kaelin: I would implore people to stop using agents with unknown mechanisms of actions. I realize we are currently limited, but I don’t know what thalidomide does, so in terms of testing a hypothesis, I don’t even know what hypothesis is being tested, because it is such an obscure agent.

Dr. Yang: I agree, although it was the only available one. In the crossover arm, those patients were going to crossover to an arm that wasn’t getting scientifically tested otherwise.

Dr. Daniel George: Did you cross anybody over from 3 mg/kg to 10 mg/kg?

Dr. Yang: Not when they frankly progressed, but we did cross over one patient after 2 years of being stable on 3 mg/kg.

Dr. George: In terms of responses, were larger lesions less likely to respond than smaller lesions?

Dr. Yang: One of the people who responded had bulky, pleural-based, and parenchymal lung disease, whereas the others had relatively small disease; two of the responders had nodal disease, but again, half the patients have nodal disease, so it is hard to say whether that is really a privileged site for response.

Dr. George: We saw in our VEGF inhibitor studies some headache associated with treatment. Is headache associated with bevacizumab treatment?

Dr. Yang: That didn’t show up on this study, because headache was also present in the placebo group; however, the nurses felt it was definitely a toxicity during infusion.

Dr. Figlin: What percentage of patients who had prior interleukin-2 therapy had bone metastases that ultimately excluded them from this trial? I never realized before that the population of kidney cancer patients on your study was selected against those with bone metastases.

Dr. Yang: It’s not that selective, because there were two, three, and six patients in the three groups with bone disease. Maybe 10% of our patients have bone disease, so we didn’t really exclude that many.

Dr. Atkins: What’s the thinking about the mechanisms of hypertension and proteinuria?

Dr. Yang: That’s something that we don’t know. Dan George and I have been discussing whether there is role of pericytes in the glomeruli accounting for changes in glomerular permeability, but again that’s not reflected in any evidence of a problem with kidney function overall. It may just be an alteration of the molecular sieving function of the glomerulus.

Dr. Gordon: One of the common hypotheses now is that it’s somehow related to endothelial nitric oxide synthase. In this regard, bevacizumab might counteract the hypotensive process triggered by interleukin-2, perhaps adding to the attraction of such combination therapy.

Dr. Atkins: Endothelial nitric oxide synthase is regulated through the VEGF receptor on endothelial cells, so bevacizumab could be blocking its production, leading to hypertension.

Dr. George: Right, and it does look like it might be a class effect and VEGF related, whether that is direct or indirect.

Dr. Atkins: Did you see any skin toxicity, particularly hand-foot toxicity?

Dr. Yang: No.

Dr. George: We had one patient with a nonspecific grade 2 hand-foot rash on PTK787.

Dr. W. Marston Linehan: Did you see anything in bone metastases that suggested response?

Dr. Yang: No, but we had fewer than a dozen patients with bone metastases.

REFERENCES

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