

IN FOCUS: RENAL CELL CARCINOMA

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Anti-VEGF Therapy for Renal Cell Carcinoma

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H&O What is the background of the research with anti-VEGF therapy in renal cell carcinoma?

BE There is a strong rationale for the use of anti-vascular endothelial growth factor (VEGF) therapy in renal cell carcinoma. It is known that in kidney cancer, the loss of Von Hippel-Lindau (VHL) protein typically activates VEGF expression. VEGF is highly overexpressed in this disease; in fact, kidney cancer is the disease with the highest overexpression of VEGF among all cancers. VEGF expression levels are strongly correlated with prognosis and survival. High levels of VEGF are associated with comparatively shorter survival. For all these reasons, over the past several years, many researchers have hypothesized that blocking VEGF would be a valid treatment for kidney cancer. In fact, among all the antiangiogenic agents tested in kidney cancer, the monoclonal antibody bevacizumab (Avastin, Genentech) was the first tested and shown to be active in this setting. The initial study of this agent was sponsored by the National Cancer Institute and compared bevacizumab with placebo after failure of interleukin-2. Patients were randomized to either bevacizumab 10 mg/kg every 2 weeks, bevacizumab 3 mg/kg every 2 weeks, or placebo every 2 weeks. When looking at progression-free survival, a very significant improvement was observed in the highest-dose bevacizumab arm compared with placebo. Based on these data and the anti-VEGF rationale, the phase III AVOREN trial was initiated to investigate the use of bevacizumab in combination with interferon- α 2a (IFN) versus IFN alone as first-line therapy in patients with metastatic renal cell carcinoma.

H&O What were the findings of this research?

BE The first-line combination of bevacizumab and IFN was tested in nephrectomized patients with clear-cell carcinoma, which comprises the largest proportion of kidney cancer patients and also is associated with the activation of VEGF through the VHL mutation. When bevacizumab was added to IFN compared to IFN plus placebo, tumor shrinkage, which was the objective response rate, increased from 13% to 31% ($P < .0001$). Second, progression-free survival doubled, from 5.4 to 10.2 months (hazard ratio, 0.63; $P < .0001$). Finally, there was a strong trend toward improvement of overall survival ($P = .0670$), although it did not yet reach significance. Overall survival data will be available in approximately 1 year.

H&O What doses were used in this trial?

BE Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, and IFN was administered three times a week at a recommended dose of 9 MIU for up to 1 year. However, it must be noted that in different tumor types, the recommended doses of bevacizumab vary from 7.5 to 15 mg/kg. I believe there is no strong rationale to use one dose over another. Research is needed to elucidate what is the active dose. Is the active dose the one that blocks VEGF, and, thus, should VEGF levels be monitored during administration of this therapy? It is not known whether every patient should receive the same dose. Additionally, it is not known whether the dose should be increased if there is insufficient blockage of VEGF.

H&O What toxicities were observed in this trial?

BE There were not many surprises in the toxicity profile of the treatment; some side effects were attributable to IFN and some to bevacizumab. Hypertension was observed

at rates similar to those observed with bevacizumab alone in other cancers. Grade 3–4 toxicities were in the range of 2–5%, with the exception of grade 3–4 hypertension, which was seen at a rate of a little less than 10%. The only toxicity that was higher in the combination arm was grade 3 fatigue. It is not known if this increase of grade 3 fatigue in the combination arm is due to an additive effect or to the longer treatment period with IFN. The combination therapy was acceptable in terms of toxicity in most of the patients.

H&O Was the treatment ineffective in any subgroups?

BE Yes. When we analyzed the data from the different subgroups, we were unable to show a statistical benefit in the poor-risk group, based on Memorial Sloan-Kettering Cancer Center classification. In this group, although it included only 50 patients (of a total population of 641 treated), there was no difference in progression-free survival. Based on this finding, if we had to make a recommendation for patient selection, we would include only the good- and intermediate-risk subgroups to receive bevacizumab plus IFN for the first-line treatment of metastatic clear-cell carcinoma of the kidney.

H&O What are the next steps in research with bevacizumab in renal cell carcinoma?

BE I foresee two important steps in future research in this setting. First, one question to answer is whether it is necessary to employ IFN in combination to achieve the positive effects seen. How much of these effects are due to bevacizumab and how much to IFN in combination with bevacizumab? Many researchers believe that the positive results seen with this combination are due to the anti-VEGF effect of bevacizumab, but it is likely some of the results can be attributed to IFN. It is necessary to know whether IFN should be given for such a long time. In

the AVOREN trial, it was administered for up to 1 year, which may not be necessary, especially in patients who have not achieved partial or complete remission. Thus, it is necessary to compare bevacizumab alone to this combination regimen in order to discern if there is an additive effect. The second step of research is to assess the use of bevacizumab in combination with other targeted agents. It seems that bevacizumab is the best drug to combine with other targeted agents. At June's annual meeting of the American Society of Clinical Oncology, data were presented from phase I trials of temsirolimus (Torisel, Wyeth) plus bevacizumab and sunitinib (Sutent, Pfizer) plus bevacizumab. Such combinations are clinically feasible, and, from these phase I results, these combinations seem very active in terms of response rate. It is necessary to continue to prospectively test the combination of bevacizumab and other targeted agents in order to see if response, complete remission, and perhaps cure rates can be improved.

Suggested Readings

Escudier B, Koralewski P, Pluzanska A, et al. A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon- α 2a vs placebo/interferon- α 2a as first-line therapy in metastatic renal cell carcinoma. *J Clin Oncol*. 2007;25(18S pt 1): Abstract 3.

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