**RENAL CELL CARCINOMA IN FOCUS**

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**Biomarkers: Hypertension Following Anti-angiogenesis Therapy**

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**H&O** What is the relationship between hypertension and angiogenesis inhibitors that target vascular endothelial growth factor (VEGF)?

**BR** The relationship between hypertension and anti-VEGF agents is a complicated one. Generally speaking, we know that agents that inhibit angiogenesis—VEGF inhibitors in particular—cause hypertension as a side effect. This represents an on-target side effect, meaning that it is a direct result of VEGF or VEGF receptor inhibition. The incidence of hypertension during anti-VEGF therapy is approximately 30–40%, of which approximately 5–10% would be grade 3 or higher, depending on the agent used. A fair amount of retrospective data have now demonstrated that patients who developed treatment-induced hypertension have a superior clinical outcome compared to patients who did not. In the study, approximately 66–75% of patients reached that blood pressure marker. We found that for objective responses—progression-free survival (PFS) and overall survival (OS)—there were superior clinical outcomes across the board. A similar association was observed with diastolic blood pressure, although it did not seem to be as strong. Why that is has not been clarified, and speculating about that difference would be difficult because we do not fully understand the mechanism of this phenomenon.

**H&O** In this analysis, did the management of hypertension during therapy have any effect?

**BR** It did not. We looked at people who were managed by dose reduction, addition of antihypertensive medications, both of these maneuvers, or neither maneuver, and did not find that the type of hypertension management affected clinical outcome. However, it must be noted that each of these subsets had a small number of patients, which was a limitation.

**H&O** Did the presence of hypertension at baseline affect clinical outcome?

**BR** This question highlights the limitations of any retrospective analysis. In our analysis, baseline blood pressure eligibility criteria were not uniform among the many trials included—some were more specific, some were nonspecific. Therefore, we observed variable blood pressure measurements at baseline. Because this analysis was retrospective, we could not control for that.
That said, the presence of baseline hypertension did seem to be a factor, and it may speak to the fact that this association may be a host effect. These differences in the association of hypertension and clinical outcome may be in part due to the type of patient—patients who are susceptible to hypertension at baseline are susceptible to the hypertensive effects of these medicines, and their tumor blood vessels are susceptible to VEGF inhibition. Again, this is just a hypothesis at this point, but that is how I would put these data together.

**H&O** Were the adverse events of therapy affected by the presence of hypertension?

**BR** The analysis expanded to look at approximately 5,000 patients who were treated not only in the prospective clinical trials but also in the compassionate use study that preceded the US Food and Drug Administration approval of sunitinib in RCC patients. It seemed that the incidence of hypertension-related toxicity was very low and not different between groups for most hypertension side effects. The only signal that emerged from our analysis was renal side effects, which seemed to be greater in patients who developed hypertension. This was assessed by the mean hypertension over time; the average of blood pressures posttreatment would probably reflect the blood pressures that the end organs are seeing. Unquestionably, prospective studies are needed, but it is not surprising that patients with one kidney who have hypertension will have more renal problems.

**H&O** In your opinion, would hypertension be a viable predictive biomarker for clinical outcome?

**BR** I think it is very promising. Not only our study data, but also other retrospective data across cancer types, across mechanisms of anti-VEGF agents, and across clinical endpoints have seen that hypertension appears to correlate with outcome, accounting for time on therapy and other statistical analyses that have been applied. So, the idea seems very promising. The current challenge is to understand the mechanism of action and figure out how to exploit it, because if there is a way to identify and classify patients before they receive therapy, that would be ideal.

**H&O** Do you know of any prospective studies that are looking into this?

**BR** There is a study of axitinib (Pfizer), a compound similar to sunitinib, that is prospectively investigating somewhat the same question in terms of more careful measurement of blood pressure and correlating drug blood levels with blood pressure. Although it is thought that the association is an independent phenomenon and not just a reflection of higher blood drug levels, this needs to be prospectively validated. There were data on axitinib that were presented at the 2008 American Society of Clinical Oncology meeting—from a retrospective analysis of 6 phase II trials that looked at basically the same parameters: clinical outcome and treatment-induced hypertension—that basically showed the same association. I am not aware of any other plans, but I think it is something that needs to be investigated going forward.

**H&O** What sort of study design should be kept in mind when planning a trial that investigates hypertension as a potential biomarker?

**BR** We need more careful assessment of blood pressure and more blood pressure assessment prior to therapy. The retrospective trials that are included in these analyses have, by and large, only 1 baseline blood pressure measurement, which can be subject to variability depending on multiple factors such as time of day or patient pain and anxiety level. When new trials are being designed in this field of study, researchers need to be aware of the importance of frequent blood pressure assessments before and during therapy and the monitoring of the correlation between blood drug levels and efficacy.

**Suggested Reading**

