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NEWS & ANALYSIS

Sunitinib-Induced Hypertension Linked to Superior Clinical Outcomes in Metastatic RCC

By Anne Landry | May 5, 2011

Executive Editor, *ONCOLOGY Nurse Edition*

Following a retrospective analysis which may be the largest of its kind to date, a multicenter team of investigators says treatment-related hypertension may be a useful biomarker of superior clinical outcome with sunitinib (Sutent) in patients with metastatic renal cell carcinoma (RCC).

"Median PFS and OS were more than fourfold longer for patients with hypertension than for patients without hypertension as defined by a maximum SBP of at least 140 mm Hg. In addition, ORR was more than six times greater in patients with hypertension than in patients without hypertension," the investigators reported, after conducting a pooled analysis of efficacy and safety data from four studies.

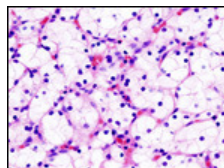
Hypertension is a well-known effect of sunitinib, which inhibits the vascular endothelial growth factor (VEGF) pathway. The mechanism by which sunitinib and other VEGF inhibitors cause hypertension is not fully understood, but hypertension is believed to result in part from direct activity of the drug on tumor vasculature (see sidebar).

Lead author Brian Rini, MD, from the Department of Solid Tumor Oncology at the Cleveland Clinic Taussig Cancer Institute, and his coinvestigators **reported their findings online in the *Journal of the National Cancer Institute* (April 28)**. Coauthors of the study are from the Royal Marsden Hospital NHS Trust, London, the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center, Los Angeles, Memorial Sloan-Kettering Cancer Center, New York, and Pfizer Oncology research and development sites in La Jolla, California, and New York.

Dr. Rini and coinvestigators retrospectively assessed the association of sunitinib-induced hypertension with both antitumor efficacy and adverse events related to hypertension in patients with metastatic RCC. The pooled efficacy (n = 544) and safety (n = 4,917) data were from four studies of patients with metastatic RCC who had been treated with sunitinib at a dose of 50 mg daily on a 4-week-on 2-week-off schedule. Blood pressure had been measured in the clinic on days 1 and 28 of each 6-week cycle.

Hazard ratios (HR) for survival were estimated by a Cox proportional hazards models using hypertension (maximum systolic blood pressure [SBP] ≥ 140 mm Hg or diastolic blood pressure [DBP] ≥ 90 mm Hg) as a time-dependent covariate. The Cox model was also used to assess the influence on PFS and OS of selected baseline prognostic risk factors (Memorial Sloan-Kettering Cancer Center criteria and criteria developed for patients with metastatic RCC receiving VEGF inhibitors). Kaplan-Meier methods were used to estimate progression-free survival (PFS) and overall survival (OS) in these patients.

By the end of cycle 1 of treatment, 58% of patients had systolic-defined hypertension and



Histopathologic image of clear cell carcinoma of the kidney. Nephrectomy specimen. Hematoxylin-eosin stain. Source: Wikimedia Commons user KGH

Anti-VEGF Treatment and Hypertension in Renal Cell Cancer

Dr. Brian Rini and coinvestigators, reporting in *JNCI* on April 28 on a retrospective analysis of associations between treatment with sunitinib (Sutent), hypertension, and safety and clinical outcome in patients with metastatic renal cell cancer, noted that further investigation is required to determine the precise mechanism by which inhibition of vascular endothelial growth factor (VEGF) may cause hypertension.

Recent research, they said, has shed some light on this question, however: Antagonism of VEGF, they said, has been found to decrease nitric oxide production, which in turn causes vascular constriction and reduces renal excretion of sodium ions, resulting in hypertension.

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- Breast
- Breast (HER2+)
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- CML
- Colorectal
- Gastrointestinal
- GIST
- Genitourinary
- Gynecologic
- Head & Neck
- Hematology
- Kidney (Renal Cell)
- Leukemia
- Lung
- Lymphoma
- Melanoma
- Ovarian
- Pancreatic
- Prostate
- Sarcoma

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- Complications
- End-of-Life Care
- Palliative Care

More Topics

- Ethics in Oncology
- Practice Management
- Practice & Policy

All Topics ►

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48% had diastolic-defined hypertension. By the end of cycle 2, 80% had systolic-defined hypertension and 68% had diastolic-defined hypertension. The median post-baseline SBP to DBP ratio in patients with hypertension was 160 mm Hg over 98 mm Hg. In patients without hypertension, the median post-baseline SBP to DBP ratio was 130 mm Hg over 82 mm Hg.

In comparing clinical efficacy and adverse events between patients with and without hypertension, the investigators found better clinical outcomes in those with sunitinib-induced hypertension (as defined by maximum SBP), compared with patients who did not have treatment-induced hypertension. The objective response rate (ORR) was 54.8% vs 8.7%, median PFS was 12.5 months vs 2.5 months, and OS was 30.9 months vs 7.2 months, respectively ($P < .001$ for all outcomes). Results were similar for patients who had sunitinib-induced hypertension defined by maximum DBP.

In a Cox proportional hazards model using hypertension as a time-dependent covariate, PFS and OS were improved in patients with treatment-induced hypertension defined by maximum SBP, with risk of disease progression or death reduced by about 40% (HR = .603) and risk of death reduced by about 67% (HR = .332). While OS was improved in patients with treatment-induced HTN as defined by maximum DBP (HR of death = .585), PFS was not improved.

Graphical analysis of PFS and OS “demonstrated that patients with hypertension (as defined by a maximum SBP of at least 140 mm Hg) continued to survive longer than patients without hypertension, independent of use of antihypertensive agents, hypertension-induced dose reductions, or both,” the study authors said. Although rates of adverse events were similar in those with and without hypertension defined by mean SBP, more renal adverse events occurred in the hypertensive patients (5% vs 3%; $P = .013$), and the

investigators said this finding warrants further investigation. Few cardiovascular, cerebrovascular, ocular, and renal adverse events of any cause were observed.

In conclusion, Dr. Rini and his coinvestigators wrote that “[i]n patients with metastatic renal cell carcinoma, sunitinib-associated hypertension is associated with improved clinical outcomes without clinically significant increases in hypertension-associated adverse events, supporting its viability as an efficacy biomarker,” as well as providing “further support to the growing body of evidence that VEGF pathway inhibitors are associated with treatment-induced hypertension, which, in turn, may be a correlative biomarker of antitumor efficacy.”

They noted, however, that development of hypertension while receiving treatment with sunitinib “was neither necessary nor sufficient for clinical benefit in all patients.”

In their article in *JNCI*, the investigators described the limitations to their study, including the fact that relative sunitinib dose intensity and cumulative sunitinib dose were only weakly correlated with maximum blood pressure. Also, they wrote, recent research by other investigators suggests “substantial interpatient variability in DBP elevation at given sunitinib trough plasma concentrations, in predominantly patients with renal cell carcinoma.” They emphasized that “further studies are warranted to confirm that sunitinib-induced hypertension is a ‘true’ biomarker of efficacy and not simply an epiphenomenon of higher drug exposure, a possibility that cannot be definitively excluded given the inherent limitations of a retrospective analysis.”

In discussing management of patients with metastatic RCC, the authors emphasized the importance of aggressively monitoring them for sunitinib-induced hypertension “and treating them as necessary with antihypertensive medication, as recently recommended by an expert panel of the National Cancer Institute for patients receiving VEGF inhibitors.”

The study was supported by funding from Pfizer, Inc.

Also, they noted, a recent study found treatment with sunitinib was linked to a statistically significant reduction of capillary density ($P < .01$) that was significantly correlated with changes in blood vessel morphology as well as increased systolic and diastolic blood pressure, which were statistically significantly associated with prolonged progression-free survival ($P = .044$). And research conducted over the past few years indicates that other renovascular mechanisms may be involved, Dr. Rini and coinvestigators said.

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