Axitinib and sorafenib in second-line treatment of advanced renal cell carcinoma

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Axitinib is a second-generation inhibitor of vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3 that exhibits increased potency in VEGFR inhibition and reduced off-target effects compared with first-generation inhibitors. The phase 3 AXIS trial recently compared axitinib with the VEGFR inhibitor sorafenib in the second-line treatment of advanced renal cell carcinoma (RCC). The trial is the first phase 3 trial to directly compare antiangiogenesis agents in this setting.[1]

In AXIS, 723 patients aged 18 years or older with advanced RCC that had progressed despite initial systemic therapy were randomized to receive axitinib (361 patients) or sorafenib (362 patients). Patients had to have cytologically or histologically confirmed RCC with a clear-cell component and measurable disease. Previous therapy had to include sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines, and it had to have ended at least 2 weeks before study entry or at least 4 weeks before entry if the previous treatment was bevacizumab plus interferon-alfa. If the starting axitinib dose of 5 mg twice daily was tolerated, then patients could have the dose increased to 7 mg twice daily after 2 weeks and subsequently to 10 mg twice daily; the dose could be decreased to 3 mg twice daily and then to 2 mg twice daily. Sorafenib was given at 400 mg twice daily, which could be decreased to 400 mg once daily or every other day. The primary endpoint of the study was progression-free survival (PFS).

The patients had a median age of 61 years. The axitinib and sorafenib groups were well matched for sex (71% and 73% men, respectively), ethnic origin (77% and 74% white), ECOG performance status (0 in 54% and 55%), and Memorial-Sloan Kettering Cancer Center (MSKCC) risk assessment (favorable in 28% and poor in 33% in both groups). Previous systemic therapy included sunitinib in 54%, cytokines in 35%, bevacizumab in 8%, and temsirolimus in 3% of patients in each group.

At the time of data cut-off, 61% of axitinib patients and 71% of sorafenib patients had discontinued the study treatment, with the most common reason for discontinuation being disease progression. Patients received axitinib for a median of 6.4 months (range, 0.03-22 months), and sorafenib for a median of 5.0 months (range, 0.03-20 months). The mean dose intensity (actual total dose/intended total dose) was 99% in the axitinib group and 92% in the sorafenib group. One or more dose interruptions occurred in 77% of axitinib patients and in 80% of sorafenib patients; dose

What's new, what's important

The Food and Drug Administration recently approved axitinib, a second-generation inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, as a second-line treatment for advanced renal cell carcinoma. The agency based the approval on the phase 3 findings of the AXIS trial in which investigators compared the multikinase inhibitors axitinib with sorafenib in patients who had received previous therapy with sunitinib, bevacizumab, cytokines, or temsirolimus.

The median progression-free survival was 6.7 months in the axitinib group and 4.7 months in the sorafenib group ($P < .0001$), though among patients who had previously received a cytokine-based therapy, the difference in median PFS between the 2 drug groups was greater—12.1 months for axitinib and 6.5 months for sorafenib ($P < .0001$). While that difference might seem encouraging, one needs to be mindful that about a third of the patients had previous cytokine therapy and that immunotherapies such as the cytokines are being replaced by targeted therapies. Overall survival has not yet been reported. As Hirsch and Daniel note in their Commentary on page 212, the AXIS results are sufficient to support the use of axitinib as a second-line therapy over other TKIs, though questions remain about the use of sequential TKIs and especially the oral mTOR everolimus. Axitinib or everolimus could be used in patients who are resistant to first-line sunitinib.

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reductions occurred in 31% and 52% of patients, respectively. An axitinib dose increase to > 5 mg twice daily occurred in 37% of patients.

The median PFS was 6.7 months in the axitinib group, compared with 4.7 months in the sorafenib group, representing a significant 33% reduction in risk for progression (hazard ratio [HR], 0.665; 95% confidence interval [CI], 0.544-0.812; $P < .0001$). Among patients who were previously treated with a cytokine-based regimen, the median PFS was 12.1 months with axitinib, compared with 6.5 months with sorafenib, representing a significant 54% reduction in risk of progression (HR, 0.464; 95% CI, 0.318-0.676; $P < .0001$). Among those previously treated with a sunitinib-based regimen, PFS was 4.8 months with axitinib, compared with 3.4 months with sorafenib, yielding a significant 26% risk reduction (HR, 0.741; 95% CI, 0.573-0.958; $P = .017$). Other subgroup analyses, including analyses by age, sex, MSKCC risk group, and study region, showed a consistent advantage for axitinib. Objective response rates were 19% with axitinib and 9% with sorafenib ($P = .0001$), with median durations of response of 11 months and 10.6 months, respectively. Data on overall survival are not yet mature.

Discontinuation of treatment because of adverse events occurred in 4% of axitinib patients and in 8% of sorafenib patients. The most common clinical adverse events of any grade (occurring in > 30% of patients) were diarrhea, hypertension, fatigue, decreased appetite, nausea, and dysphonia in axitinib patients and diarrhea, palmar-plantar erythrodysesthesia, fatigue, rash, and alopecia in sorafenib patients. Hypertension, nausea, dysphonia, and hypothyroidism were more common with axitinib, and palmar-plantar erythrodysesthesia, alopecia, and rash were more common with sorafenib. The most frequent adverse events of grade 3 or higher in axitinib patients were hypertension (16%), diarrhea (11%), fatigue (11%), decreased appetite (5%), palmar-plantar erythrodysesthesia (5%), and asthenia (5%); and in sorafenib patiets, palmar-plantar erythrodysesthesia (16%), hypertension (11%), diarrhea (7%), and fatigue (5%).

The most common laboratory abnormalities of any grade (occurring in > 30% of patients) were creatinine elevation, hypocalcemia, anemia, and lymphopenia in axitinib patients and hypocalcemia, anemia, hypophosphatemia, lipase elevation, creatinine elevation, and lymphopenia in sorafenib patients. Hemoglobin elevation and creatinine elevation were more common with axitinib and anemia, hypophosphatemia, hypocalcemia, and lipase elevation were more common with sorafenib. The most frequent laboratory abnormalities of grade 3 or more were lipase elevation (5%) and lymphopenia (3%) with axitinib and hypophosphatemia (16%), lipase elevation (15%), anemia (4%), and lymphopenia (4%) with sorafenib. Elevated hemoglobin was found in 10% of axitinib patients and 1% of sorafenib patients and infrequently required management by phlebotomy. Elevations of thyroid-stimulating hormone of ≥ 10 mU/L in patients with levels < 5 mU/L at baseline occurred in 32% of axitinib patients and 11% of sorafenib patients. Supplemental thyroid medication was either started or increased in dose in 27% of axitinib patients and 14% of sorafenib patients.

Reference

1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939.