Research Highlight

Could tivozanib be a new potent pan-VEGF inhibitor in RCC therapy?

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In the course of the last decade the therapy of renal cell carcinoma (RCC) stepped into a new era as targeted therapies changed protocols and the prognosis of patients as well. Could this successful start with sunitinib and sorafenib be continued by more potent agents? Because objective response rates (ORR) are still far from ideal (none of them reach 50%), other targeted molecular approaches need to be developed. Consequently, a number of currently ongoing trials focus on confirming potential new agents for the systemic therapy of metastatic RCC (mRCC). One of these, tivozanib is a tyrosine kinase inhibitor blocking all three VEGF receptors (pan-VEGF inhibitor), thus it potentially possesses all the indications of the currently recommended Sorafenib, Pazopanib and Axitinib.

Currently used agents in second-line therapy after cytokine treatment are sorafenib and pazopanib. Sorafenib increases overall survival by 7.5 to 35 months, PFS by 5.4 to 12 months beside an ORR of 46%. For pazopanib the trials demonstrate 9.3 months progression-free survival (PFS) instead of PFS and an ORR of 20% to 32 % (1).

In a recent report in the *Journal of Clinical Oncology* by Nosov and his colleagues describe the latest results of a phase II randomized trial of tivozanib (2). The primary end points were safety, the ORR at 16 weeks, and the percentage of progression free survival of randomly assigned patients after 12 weeks of tivozanib treatment compared to a placebo treated control group. The secondary end points comprised PFS. Earlier, tivozanib activity was observed in a phase I study in which RCC patients experienced clinical benefit from treatment.

The patients (n=272) were administered tivozanib 1.5 mg/d orally for 16 weeks. Then, patients with less than 25% change in tumor size (n=118) were randomly assigned to receive either tivozanib (n=61) or placebo (n=57) for the next 12 weeks in a double-blind manner. Patients with partial response (n=78) or more than 25% tumor shrinkage could continue the open label tivozanib therapy. The remaining 76 patients discontinued the study, mainly due to progressive disease (n=51).

The ORR after 16 weeks was only 18%, but all patients had partial response (PR). Throughout the entire study though, the ORR was 24% (19% to 30%). The PFS after 12 weeks (measured from random assignment) was significantly (P=0.01) longer among patients with tivozanib treatment (10.3 months; 8.1 to 21.2 months) compared to patients receiving placebo (3.3 months; 1.8 to 8.0 months). It has to be mentioned that of the 57 patients in the placebo arm 24 completed the arm without progression, 24 patients switched to the open label tivozanib due to progressive disease and 9 patients discontinued the trial. The median PFS in all treated patients was 11.7 months (8.3 to 14.3 months) excluding the placebo arm. The study results show that in RCC patients after nephrectomy tivozanib demonstrates improved antitumor activity with an ORR of 30% (23% to 37%) and median PFS of 14.8 months (10.3 to 19.2 months) compared to patients without nephrectomy.

The 15 deaths throughout the trial were mostly the consequences of disease progression, and none of them was treatment related. The most common adverse events (AE) were hypertension (45%), dysphonia (22%), diarrhea (12%), asthenia (10%) and certain laboratory abnormalities. Although 22 patients ended the trial due to AE, side effects in grade 3 and 4 were infrequent.

We must also draw the attention to some of the

limitations of the study. The 272 enrolled patients did not come from a homogenous group (83% had clear-cell histology, 73% of the patients had nephrectomy, and 54% of the patients were treatment naive). Pharmacokinetic samples were collected from only 21 patients to measure the concentration of tivozanib. Finally, out of those who completed the double-blind trial, in the placebo arm 26 patients progressed out of 50 cases while in the tivozanib arm 23 patients progressed out of 58 - the difference between the two cohorts is only marginally significant by a chi-square test (P=0.0498, not reported by the authors).

How could we identify RCC patients gaining the most in terms of progression free survival after tivozanib treatment? In an ongoing phase III trial tivozanib and sorafenib are compared to evaluate their efficacy and safety in 517 patients with advanced RCC. The results show statistically significant improvement in PFS with a median PFS of 12.7 months in case of tivozanib compared to a median PFS of 9.1 months with sorafenib in treatment-naïve patients (3).

Could the lower prevalence of adverse events in tivozanib-treated patients be a benefit providing superiority over the currently used agents? As today more patients are being treated for longer periods of time, the management of the associated AEs is gaining importance. Eisen and his colleagues suggest an alternative solution to this issue by using improved strategies to monitor and manage patients with side effects (4).

In conclusion, the results of the tivozanib phase II trial are so far encouraging but the final data gathered during a phase III trial must settle the debate if it could become one of the recommended agents for RCC therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Mihaly Z, Sztupinszki Z, Surowiak P, et al. A comprehensive overview of targeted therapy in metastatic renal cell carcinoma. Current cancer drug targets 2012;12:857-72.
2. Nosov DA, Esteves B, Lipatov ON, et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. J Clin Oncol 2012;30:1678-85.
3. Motzer RJ, Bhargava P, Esteves B, et al. A phase III, randomized, controlled study to compare tivozanib with sorafenib in patients (pts) with advanced renal cell carcinoma (RCC). J Clin Oncol 29:2011:abstr 310.
4. Eisen T, Sternberg CN, Robert C, et al. Targeted therapies for renal cell carcinoma: review of adverse event management strategies. J Natl Cancer Inst 2012;104:93-113.

