Research Highlight

Tivozanib: is total VEGFR inhibition the way to success in terms of tolerability and efficacy in advanced kidney cancer?

Marine Gross-Goupil[1], Alain Ravaud[1,2]

[1]Saint-André Hospital, University Hospital, Bordeaux, France ; [2]Université Bordeaux 2, Victor Segalen, Bordeaux, France
Correspondence to: Marine Gross-Goupil, MD, PhD. Saint-André Hospital, University Hospital, Bordeaux, France.
Email: marine.gross-goupil@chu-bordeaux.fr.

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The family of tyrosine kinase inhibitors is still growing. After sunitinib, sorafenib and more recently pazopanib, and axitinib, we probably now should count on tivozanib (1). This pan-VEGFR inhibitor (VEGF-R1,-R2,-R3) is more selective and potent *in vitro* than previous known TK inhibitors. Tivozanib was tested in a phase II trial reported by Nosov *et al.* (1) Tivozanib was administered at a daily dose of 1.5 mg, for 3 weeks followed by a break of 1 week. Of the 272 patients treated during the first period of 16 weeks, 78, who presented tumour shrinkage of at least 25%, were maintained on tivozanib. All of the 118 patients who presented less than 25% change in the tumour, were randomized between placebo and tivozanib, during the next 12 weeks. Finally, 76 patients discontinued the treatment and were excluded from the analysis, mainly due to progressive disease (50/76). The main clinical characteristics include clear cell histology (83%), and prior nephrectomy (73%) with no previous treatment (54%). Considering all the patients, the median progression-free survival (PFS) and objective response rate (ORR) were 11.7 and 24% respectively. Results may be considered according to the two sequential periods of treatment. The ORR during the sixteen week open-label period reached 18% (95%CI, 14-23%), with 66% of stable disease (SD). At the end of the second double-blind period, significantly more patients in the tivozanib arm (49%, n=30) were progression-free, compared with the placebo-arm (21%, n=12), (P=0,001); median progression-free survival was also statistically longer in the tivozanib arm compared to placebo, 11.9 months (9.3-14.7 months) and 9.1 (7.3-9.5) respectively, HR=0.797, P=0.042. The ORR were 33% and 23% in the two groups respectively, P=0.014.

In terms of toxicity, the hypothesis suggesting that the specificity of the target would permit a decrease in off-targeted toxicity was confirmed with less adverse events apart from hypertension, a class effect. The two more frequent adverse effects of any grade reported were: hypertension (45%), and dysphonia (22%). Other toxicities, frequently reported with other TKIs, such as asthenia, diarrhea, stomatitis or hand-foot syndrome, were reported in 10%, 12%, 4% and 4% respectively, all grades. Dose-reduction concerned only 8% of the patients, and interruptions 4% (n=11). According to the data, the authors concluded that tivozanib demonstrated promising activity and an acceptable safety and tolerability profile.

Furthermore, these results are in accordance with the data presented by Robert Motzer at the ASCO 2012 meeting concerning a phase III trial, comparing tivozanib and sorafenib in the first-line setting (2). The same schedule of tivozanib was compared to 400 mg, twice daily of sorafenib continuously. The trial demonstrated a statistically significant benefit in progression-free survival in the 260 patients treated with tivozanib compared to the sorafenib group (n=257): 11.9 months (9.3-14.7 months) and 9.1 months (7.3-9.5 months) respectively, HR=0.797, P=0.042. The toxicity profile was as expected according to the results of this phase II trial, with 26% of grade 3/4 hypertension, and 21% of grade 3/4 dysphonia. The incidence of hypertension should be interpreted along with previous data reporting this effect, as a biomarker of pharmacological activity. Furthermore, its predictive role of a therapeutic effect, with sunitinib and more recently with axitinib has also been reported (3,4). Lastly, the safer toxicity profile may allow better exposure of the patient to

the drug. However, the recent titration data concerning axitinib has begun to shed light on the question of the fixed pre-defined dose of tyrosine kinase agents.

In conclusion, tivozanib is really a new anti-angiogenic drug in the landscape of treatment in RCC and not only a me-too drug as sunitinib, sorafenib and pazopanib are. The next challenge is the position in 1st line between tivozanib and axitinib, waiting for forthcoming planned trials.

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Footnote

Conflicts of Interest: Dr Ravaud is a member of European board for Astellas and chairman of the IDMC of pivotal trial TIVO-1. Dr Gross-Goupil has no conflicts of interest to declare.

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