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First line treatment of metastatic renal cell carcinoma

Two standards with different toxicity profile

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Tyrosine kinase inhibitors are de facto the more used targeted therapies for upfront treatment of metastatic renal cell carcinoma (mRCC). Among these, sunitinib and pazopanib have reported greater activity in term of progression-free survival and overall survival compared with interferon-α or placebo in two independent large phase III studies. Despite a large use in clinical practice these molecules had never been compared. The COMPARZ study recently published in the *New England Journal of Medicine* reports the results of a non-inferiority trial that comparing pazopanib to sunitinib as first line of therapy in mRCC patients. Here we report the activity and safety data of the study and we discuss several critical aspects related to the study design and possible confounding factors that may alter the results' interpretation.

Keywords: pazopanib, sunitinib, renal cancer, first line, toxicity, non-inferiority study, phase III trial

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Renal cell carcinoma (RCC) is the sixth most common diagnosis of cancer in men and the eighth in women in United States with an estimated 65 150 new cases and 13 680 deaths expected to occur in the current year.[1] In Europe, the incidence and the mortality of RCC are estimated to be 71 739 and 31 293 cases per year, respectively.[2,3]

In this tumor, two pathways have been emphasized for tumor survival and dissemination: the vascular endothelial growth factor (VEGF) with its receptor (VEGFR), and the mammalian target of rapamicin (mTOR).[4,5]

From 2006 to now, 5 VEGF/VEGFR inhibitors (sorafenib, sunitinib, pazopanib, axitinib, and bevacizumab) and two mTOR inhibitors (temsirolimus and everolimus), have been approved for treatment of mRCC superseding the cytokine-based therapy. As the result of this evidence, the prognosis of mRCC patients has notably improved: from 1999 to 2009, the median overall survival has increased from 10 to 22 mo.[6,7]

Currently, in patients with good or intermediate prognosis based on MSKCC criteria,[6] the use of antiangiogenic agents such as sunitinib, pazopanib, and bevacizumab plus interferon-α (IFN-α) is recommended by the major American and European guidelines, as the first-line treatment.[8,9] Despite this, use of bevacizumab in clinical practice has been reduced considering several factors such as the intravenous infusion and the concomitant administration with subcutaneous interferon then oral tyrosine kinase inhibitors are de facto the more used targeted therapies.

In the phase III trial comparing sunitinib 50 mg/day for 4 weeks followed by 2 weeks of rest to IFN-α as first line of therapy in 750 untreated patients. Sunitinib reported a decrease of the risk of progression by 58% (HR: 0.42; 95% CI, 0.32 to 0.54; $P < 0.001$) corresponding to an increase of median PFS from 5 to 11 mo with a higher objective response rate compared with IFN-α (31 vs. 6%; $P < 0.001$).[10,11]

The pazopanib phase III trial compared the activity of pazopanib 800 mg/day to the placebo in a non-homogeneous group of patients, including 233 treatment-naïve and 202 pre-treated with IFN-α.

Pazopanib was able to decrease the risk of progression both in treatment-naïve (HR: 0.40; 95% CI, 0.27 to 0.60; $P < 0.001$), and in pre-treated (HR: 0.54; 95% CI, 0.35 to 0.84; $P < 0.001$) with an increase of median PFS from 2.8 to 11.1 and from 4.2 to 7.4 mo, respectively.[12]

Despite this evidence, both treatments did not show any increase of median OS because of several reasons such as the number of patients who crossed over to the experimental treatment and the higher number of patients who received subsequent lines after disease progression.

The COMPARZ study recently published in the *New England Journal of Medicine* reports the results of a non-inferiority trial that compared pazopanib to sunitinib as first line of therapy in mRCC patients.[13]

In this study, 1100 patients have been randomized 1:1 to receive pazopanib or sunitinib at the standard dosage until progression or intolerable toxicity. Patients were stratified based on previous nephrectomy, value of lactate dehydrogenase, and Karnofsky performance status at baseline. The primary end-point of the study was to report a non inferiority of pazopanib compared with sunitinib with the upper bound of the confidence interval fixed to <1.25. Secondary end-points were the objective response rate, the overall survival and the health-related quality of life.

Results showed a median PFS of 8.4 and 9.5 mo for pazopanib and sunitinib, respectively with an HR of 1.05 and lower and higher bounds of the 95% confidence interval of 0.90 and 1.22, respectively. Then, the study met the primary end-point reporting the non-inferiority of pazopanib compared with sunitinib.

About secondary end-points the objective responses were observed in 31% of patients treated with pazopanib and in 25% of patients treated with sunitinib ($P = 0.03$). No significant differences in overall survival were observed with 28.4 and 29.3 mo for pazopanib and sunitinib, respectively (HR: 0.91; 95% CI, 0.76 to 1.08; $P = 0.28$).

Despite the positive results reached, this study records an interesting event during its conduction: because it was calculated a total of 631 disease progression events to have 80% power to reject the null hypothesis (upper bound of HR ≥1.25), then a number of 876 patients were initially considered sufficient to observe the required events. Unfortunately, the planned number was not reached, and the investigators decide to increase the sample to 1100 patients. Rather re-open the enrollment in the centers initially involved in the study, the investigators decide to include in the original trial the patients enrolled in another trial (NCT01147822) conducted only in China and Taiwan and South Korea with the intent to reach enough Asian patients to have regulatory reimbursement in these countries. Even if patients enrolled in the latter study have the same inclusion/exclusion criteria initially planned for the original trial, and the decision was applied per protocol amendment, the procedure result is quite singular. The question is if this may have influenced the quality of the final data, considering recent evidence that suggested no differences in terms of efficacy between Asian and non-Asian patients treated with TKIs but significant differences in treatment discontinuation due to adverse events, which are higher in non-Asian patients.[14]

The COMPARZ trial not only showed the non-inferiority of pazopanib over sunitinib but also reported useful data about the patients' compliance and about their toxicity profile. In the registrative trials were reported discontinuation rates due to adverse events for sunitinib and pazopanib of 19% and 16%, respectively; in the COMPARZ trial, the discontinuation rate was 20% for sunitinib and 24% for pazopanib. The incidence of common adverse events (>10% of subjects) was found to be more frequent in the sunitinib arm, and among these hand–foot syndrome (29% vs. 50%), mucosal inflammation (11% vs. 26%), hypothyroidism (12% vs. 24%), and fatigue (55% vs. 63%). The events most frequent in the pazopanib arm were: hair color change (30% vs. 10%); weight loss (15% vs. 6%), and alopecia (14% vs. 0%). Hematological adverse events were more frequent in the sunitinib arm: these were anemia (31% vs. 60%), leukopenia (43% vs. 78%), and thrombocytopenia (41% vs. 78%). Pazopanib reported an increase of hepatic toxicity with an increase of ALT (60% vs. 43%) and total bilirubin (36% vs. 27%) even if the majors differences were in high-grade hepatic toxicities for AST (12% vs. 3%), and ALT (17% vs. 5%), confirming the data of recent metaanalysis.[15]

About the direct applicability of these result in clinical practice, a recent work by Heng et al. reported the differences in terms of prognosis between patients with clinical characteristic meeting general inclusion criteria for clinical trials and who did not, with a poor prognosis for the last category.[16] In this case, the longer use of sunitinib have offered more data about efficacy and safety in patients from clinical practice.[17] With the same intent, the Principal study (NCT01649778) aims to evaluate prospectively the activity and safety of pazopanib in a large unselected population and plans to enroll approximately 700–1000 patients.

Finally, the COMPARZ trial reports the non-inferiority of pazopanib over sunitinib in first-line treatment of mRCC and it offers to physicians another molecule for metastatic patients and the possibility to choose based on drugs' safety profile without any efficacy reduction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49:1374-403; PMID:23485231; http://dx.doi.org/10.1016/j.ejca.2012.12.027
3. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013; 132:1133-45; http://dx.doi.org/10.1002/ijc.27711; PMID:22752881
4. Gunningham SP, Currie MJ, Han C, Turner K, Scott PA, Robinson BA, Harris AL, Fox SB. Vascular endothelial growth factor-B and vascular endothelial growth factor-C expression in renal cell carcinomas: regulation by the von Hippel-Lindau gene and hypoxia. Cancer Res 2001; 61:3206-11; PMID:11306510
5. Palazzo A, Iacovelli R, Cortesi E. Past, present and future of targeted therapy in solid tumors. Curr Cancer Drug Targets 2010; 10:433-61; PMID:20384576; http://dx.doi.org/10.2174/156800910791517145
6. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999; 17:2530-40; PMID:10561319

7. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, Eigl BJ, Ruether JD, Cheng T, North S, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009; 27:5794-9; PMID:19826129; http://dx.doi.org/10.1200/JCO.2008.21.4809
8. National Comprehensive Cancer Network (NCCN) mRCC guidelines available at: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf (last access: October 23th, 2013).
9. European Society of Medical Oncology (ESMO). mRCC guidelines available at: http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Urogenital-Cancers/Renal-Cell-Carcinoma (last access: October 23th, 2013).
10. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356:115-24; PMID:17215529; http://dx.doi.org/10.1056/NEJMoa065044
11. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27:3584-90; PMID:19487381; http://dx.doi.org/10.1200/JCO.2008.20.1293
12. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28:1061-8; PMID:20100962; http://dx.doi.org/10.1200/JCO.2009.23.9764
13. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013; 369:722-31; PMID:23964934; http://dx.doi.org/10.1056/NEJMoa1303989
14. Wang Y, Choueiri TK, Lee JL, Tan MH, Rha SY, North SA, Kollmannsberger CK, Heng DYC. Vascular endothelial growth factor (VEGF) therapy in metastatic renal cell carcinoma (mRCC): Differences between Asian and non-Asian patients. J Clin Oncol 2012; 30: suppl 5; abstr 451
15. Iacovelli R, Palazzo A, Procopio G, Santoni M, Trenta P, de Benedetto A, Mezi S, Cortesi E. Incidence and relative risk of hepatic toxicity in patients treated with antiangiogenic tyrosine kinase inhibitors for malignancy. Br J Clin Pharmacol 2013; (Forthcoming); PMID:23981115; http://dx.doi.org/10.1111/bcp.12231
16. Heng D, Choueiri TK, Lee JL, Harshman LC, Bjarnason GA, Knox JJ, MacKenzie MJ, Vaishampayan UN, Tan MH, Rha SY, et al. A multicentered population-based analysis of outcomes of patients with metastatic renal cell carcinoma (mRCC) who do not meet eligibility criteria for clinical trials. J Clin Oncol 2012; 30: suppl 5; abstr353
17. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, Hariharan S, Lee SH, Haanen J, Castellano D, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009; 10:757-63; PMID:19615940; http://dx.doi.org/10.1016/S1470-2045(09)70162-7