Cabozantinib in advanced non-clear-cell renal cell carcinoma: is it the way clearer now?

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Martínez Chanzá *et al.* (1) investigated the activity of cabozantinib (an inhibitor of multiple tyrosine kinase receptors) in a multicentre, retrospective, cohort study carried out by 22 centres that involved 122 patients with metastatic renal cell carcinoma (RCC) with confirmed non clear cell histology treated in any line of therapy between 2015 and 2018. In particular, the histologies were divided as follows: 59% papillary histology, 15% Xp 11.2 translocation, 13% unclassified histology, 9% chromophobe histology and 4% collecting duct histology. About 27% among these patients had an objective response to treatment [defined as the best radiological complete or partial response (PR) according to RECIST criteria]. At a median follow up of 11 months the median progression-free survival (PFS) was 7.0 months with a median overall survival (OS) of 12.0 months. The median time to treatment failure was 6.7 months (discontinuation of cabozantinib occurred mainly because of progressive disease in 85% of patients and, secondly, because of toxicity in 7% of patients). Cabozantinib was administered at the approved dose of 60 mg one time a day to 83% of patients and the main side effects of any grade related to the treatment were similar to those seen with other TKIs (tyrosine kinase inhibitors) such as fatigue (52%), diarrhea (34%), rash and palmar-plantar erythrodysesthesia (31%), nausea (29%), hypertension (28%). In general, side effects were mostly mild to moderate and were generally manageable through the standard clinical practice. No deaths related to treatment were detected. Finally, next-generation sequencing (NGS) analysis were performed in 48% of patients which demonstrated that the most common somatic genetic alterations among all tumours were cyclin-dependent kinase Inhibitor 2A (CDKN2A) (22%) followed by mesenchymal epithelial transitions (MET) (20%). The authors concluded that cabozantinib showed encouraging activity and tolerable toxicity in all non-clear cell RCC, both in treatment-naïve patients and in heavily pretreated patients (24% of patients had had three or more previous systemic therapies) and the efficacy was maintained also in patients with poor-risk or intermediate-risk disease. These results connote that the antitumour efficacy of cabozantinib is not confined to clear cell histology only.

Cabozantinib is a TKI that targets several receptors such as vascular endothelial growth factor receptors 1–3 (VEGFR 1–3), MET, AXL receptor tyrosine kinase (AXL) (2). Up to date, two large phase III trials (the METEOR trial (3) that compared cabozantinib with everolimus in patients progressed after previous VEGR-targeted therapy and the CABOSUN trial (4) that compared cabozantinib versus sunitinib as first-line therapy) evaluated the activity and safety of cabozantinib in renal cancer patients with clear cell histology or at least a clear cell component. Based on the result of these trials, it has been speculated that cabozantinib may be considered a valid option also for non-clear cell histologies, that account for 10–20% of all RCC.

However, the treatment of non-clear cell RCC is very challenging because non clear cell RCC involve many histologies which are profoundly different according to prognosis, morphological and clinical characteristics, and genetic features (5,6). Papillary RCCs is divided into type 1, often sporadic and associated with epidermal growth factor receptor or alternatively MET mutations, and type 2, mostly associated with SETD2 mutations, CDKN2A mutations, TFE3 fusions or fumaratehydratase (FH) mutations, and characterised by aggressive phenotype and often positive family history (7,8). In chromophobe RCCs the most commonly oncogenic pathway implicated is mammalian target of rapamycin (mTOR) associated with tumour suppressor protein 53 (TP53) alterations (8-10). It has been reported that papillary and chromophobe histology account for 80% of non-clear cell RCC (5,6). Collecting duct carcinoma (CDC) is a rare and extremely aggressive RCC that develop, as its name suggests, from the renal collecting ducts and is distinguished by an immune profile with a high percentage of tumour infiltrating lymphocytes (11).

The optimal treatment strategy for metastatic non clear cell RCC is still generally inferred from the evidence available for metastatic clear cell RCC. Unfortunately, due to the rarity of non-clear cell RCC tumours, only few prospective randomised trials have been carried out to date. In 2016, the results of two prospective phase II randomised trials (ASPEN and ESPN) have compared the activity of the VEGF-TKIs (sunitinib) to the mTORi (everolimus); both studies have shown improved PFS in the first line in patients treated with sunitinib. On the other hand, this benefit was not confirmed as regards the OS (12,13). Concerning the comparison between the survival outcomes for the metastatic non clear cell RCC group compared to the metastatic clear cell RCC group, a large retrospective analysis of the International Metastatic RCC Database Consortium (IMDC) (14) showed that the entire non clear cell RCC group had a worse OS than the clear cell RCC group; the median OS was 12.8 months versus 22.3 months in clear cell RCC ($P<0.0001$). By contrast, the chromophobe non clear cell RCC subtype had a survival outcome which was comparable to clear cell RCC, except for the chromophobe tumours with sarcomatoid features which are associated with poor prognosis (15).

In addition, a recent retrospective study, although involving only Asian patients (16), confirmed that the survival outcomes for the metastatic non clear cell RCC cohort were significantly inferior to the outcomes for the metastatic clear cell RCC cohort regarding to first-line PFS, total PFS, and cancer specific survival (CSS), except for the chromophobe and Xp 11.2 translocation groups that showed better survival outcomes compared to clear cell RCC. Contrariwise, first line PFS, total PFS and CSS for the other histologies evaluated in this study (like the collecting duct, papillary, and unclassified groups) were meaningfully poorer compared to those of the group clear cell RCC. Another retrospective study carried out by Koshkin *et al.*, whose results were presented at the American Society for Clinical Oncology (ASCO) genitourinary (GU) conference in San Francisco in 2017, demonstrated the activity and safety of nivolumab in non-clear cell RCC subtypes (17). Twenty-three patients with metastatic non clear cell RCC were treated with nivolumab between 12/2015 and 01/2017. The most represented histologies were unclassified (48%) and papillary (44%) and most patients had been pretreated with systemic therapy (mainly sunitinib, pazopanib or axitinib). After a median follow up of 6.5 months, median PFS was 4.2 months and median OS was not reached. Twenty-nine percent patients had PR as the best radiological response and 19% had stable disease (SD). Median time to best response was 5.1 months (17).

With regard to cabozantinib, a retrospective study demonstrated a promising efficacy in patients with metastatic non clear cell RCC with a 14.3% of patients who had confirmed PR, and 64.2% who had SD. The median PFS was 8.6 months and the median OS was 25.4 months at a median follow-up of 20.6 months (18).

Despite its clear importance and value, the study by Martínez Chanzá *et al.* presents several limitations that we have to address. First of all, the retrospective analysis could cause possible selection bias. In addition, we have to mention the population heterogeneity regarding histology and clinical history, even if the cohort analyzed is correctly evocative of the actual population treated in clinical practice. It is quite important to mention the lack of central pathological and radiological review and the use of the time to treatment failure rather than the progression free survival as one of the main endpoint (by reason of the discontinuation of the treatment that was not necessarily due to tumour progression, but rather to the physician's judgment based on patient tolerability and clinical benefit). To conclude, the ability to evaluate the efficacy of cabozantinib also in relation to the tumour genomic alterations, was possible only in a small number of patients (although this is the biggest series reported so far).

In conclusion, non-clear cell RCC includes a

heterogeneous group of tumours different from each other in terms of clinical features, genetic characteristics and prognostic variables, which are scarcely investigated due to their infrequency. It is crucial to define the efficacy of the available treatments and the best treatment sequence for this group of patients, because few studies have been carried out on the matter and it is not certain whether the data obtained for patients with clear cell histology can also be completely applied to patients with non-clear cells histology. For these reasons, the importance of the study carried out by Martínez Chanzá *et al.*, and of the other studies that have been done with similar intent, is noteworthy.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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