Optimizing renal function and outcome of patients with cT2 renal cell carcinoma

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The surgical approach to renal cell carcinoma (RCC) primary tumor and distant metastases has been the focus of a series of studies in the last years. On this scenario, Lebacle *et al.* (1) evaluated the role of neoadjuvant axitinib in cT2 RCC. They conducted an open-label, non-randomized, multicenter phase II study (AXIPAN) with the main goal of creating the favorable conditions for Partial Nephrectomy (PN) in patients with cT2 clear cell (cc)RCC. From the literature it is well known that radical nephrectomy (RN) is recommended in cases of large (>7 cm) or highly complex tumors (2), while PN is feasible in some T2 tumors (3) and can preserve a better renal function compared to RN and improve the survival rate (4). However, PN is technically challenging and requires expert surgeons.

Axitinib is an oral, vascular endothelial growth factor receptor (VEGFR)-1 to -3, c-KIT and platelet-derived growth factor receptor (PDGFR) tyrosine kinase inhibitor (TKI) approved in 2012 for the treatment of metastatic RCC after failure of prior angiogenic therapy. In the AXIPAN study, axitinib 5mg was administered twice a day, with dose titration made on individual tolerability according to standard practice. Eighteen patients were enrolled, with a mean age of 60 years and a median baseline tumor size of 76.5 mm. All of them had a cT2a N0/Nx M0 renal tumor according to the 2009 TNM classification. After axitinib neoadjuvant treatment, 89% of tumors decreased in diameter, with a median reduction of 12 mm. After a median interval of six days after treatment conclusion, a total of sixteen patients underwent PN, that was robotic-assisted in nine cases and open in the others: axitinib was able to make feasible cases where PN was initially considered not recommended, according to guidelines.

During axitinib administration, seventeen patients had adverse events (AEs) with grade 1, 2 or 3; the most frequent were fatigue, hypertension, dysphonia and hand-foot syndrome. Three of them had to discontinue the treatment due to AEs. Moreover, two patients had serious AEs, but these did not cause their discontinuation from the study. Surgical complications were graded according to Clavien's classification: five patients experienced Clavien III–V post-surgery complications, while eleven grade I or II. A patient died a month after surgery due to myocardial infarction. One month after surgery, authors observed that mean estimated glomerular filtration rate (eGFR) decreased by 11 mL/min, 86 *vs.* 97 mL/min. At 2-years follow up, the progression rate of metastatic disease was 22%.

The results obtained in the study by Lebacle *et al.* (1) arise a series of questions: (I) it is possible to personalize axitinib treatment in the neoadjuvant setting? (II) Do we have effective biomarkers of tumor response to axitinib to select cT2 RCC patients who will benefit from neoadjuvant therapy? (III) How these data can be read in the era of immunotherapy?

Precision medicine is the novel frontier of the oncology field. The possibility of personalizing the use of anti-VEGFR TKIs and immunotherapies in RCC in order to

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improve patients' outcome and avoid unnecessary toxicities has represented, in the last decade, a major focus for uro-oncologists (5-9). On January 2019, Sorich and his group (10) have explored the physiological and molecular features that drive to the variability of axitinib exposure. Basing on the evidence that a steady-state area under the plasma concentration-time curve (AUC_{SS}) >300 ng/mL/h correlates with longer progression-free survival (PFS) and overall survival (OS), they developed a pharmacokinetic model to predict patients who will fail to reach this AUC_{SS} value. They found that the variability in axitinib AUC_{SS} is mainly due to the inter-patient differences in hepatic CYP3A4 abundance and albumin concentration, suggesting these two parameters as ideal candidate for individualizing axitinib treatment in RCC (10).

At present, the research for effective and reliable biomarkers of response to axitinib has not led to practice-changing results. However, the steps forward on understanding the mechanisms of axitinib-induced cell death (characterized by senescence, mitotic catastrophe) (11,12) and on the role of this drug on immune cells (in particular on NK cells) (11) have opened the way to novel potential biomarkers of response that should be investigated in future prospective clinical trials.

Immunotherapy has completely changed the therapeutic approach to RCC (13,14). Since the approval of nivolumab (15) by the Food and Drug Administration (FDA) for previously treated patients with metastatic RCC, the number of clinical studies on the efficacy of combining immunocheckpoint inhibitors with anti-angiogenic drugs or other immunotherapies are rapidly grown, suddenly providing optimistic results in terms of disease control rate, OS and tolerability. Concerning the role of immunotherapy in the neoadjuvant setting of RCC, several trials are in course to investigate the efficacy and safety of immunocheckpoint inhibitors. Among them, two phase I trials (NCT02575222, NCT02595918) are ongoing to assess the efficacy and safety of Nivolumab as monotherapy for locally advanced or non-metastatic high-risk RCC, while a phase II study (NCT03680521) is studying the combination of Nivolumab with sitravatinib, an oral TKI that multiple pathways including VEGF, c-MET, and the Tyro3, Axl, and MER family, as neoadjuvant therapy. Furthermore, a phase I trial (NCT02212730) is exploring the effect of Pembrolizumab administered before and after nephrectomy. Otherwise, a phase II study (NCT03341845) on axitinib plus Avelumab and a phase I trial on anti-PD-L1 durvalumab in combination with anti-CTLA-4 tremelimumab are enrolling patients with locally advanced RCC (NCT02762006).

In conclusion, the phase II trial led by Lebacle *et al.* showed that neoadjuvant axitinib is feasible; its mechanism of action allows a better response on primary tumor compared to other TKIs (16,17) and favors PN over RN in baseline cT2 localized renal tumors. However, the final decision about surgery was left to surgeons and could depend on their experience, consequently there are not fixed criterion to guide this decision. Also, the authors themselves concluded asserting that although neoadjuvant axitinib is feasible in cT2 ccRCC patients and allows a tumor shrinkage <7 cm in 67% of cases, PN procedures remains complex and it could generate possible morbidity.

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Footnote

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

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