Commentary

Management of metastatic renal cell carcinoma: The complexity of choice

Jacqueline T. Brown a,b, Mehmet Asim Bilen a,b,*

*a Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA
b Winship Cancer Institute of Emory University, Atlanta, GA, USA

The landscape of metastatic renal cell carcinoma (mRCC) has changed dramatically over the last several years since the introduction of checkpoint inhibitors (CPIs) in first-line management. Several combinations of targeted therapies plus immunotherapies are approved or under clinical investigation, creating the difficult task of knowing which to choose for the recently diagnosed patient. Recognizing the lack of head-to-head randomized control trials (RCTs) to delineate between these options, Wang, et al. recently designed a network meta-analysis with focus on both treatment efficacy and safety with the goal of demystifying the crowded frontline therapy space for the oncologist [1].

RCC has long been identified as an immunogenic malignancy and the age of CPIs has ushered in the potential for durable complete responses and improved safety profiles that were not afforded by targeted mono-therapies against vascular endothelial growth factor (VEGF) receptors and mammalian target of rapamycin. A phase III trial of nivolumab plus ipilimumab showed improved survival and objective response rates (ORR) over sunitinib in intermediate- and high-risk patients and became standard-of-care frontline treatment in this population after FDA approval in April 2018 [2]. We soon observed that simultaneous targetting of the angiogenic and immunologic pathways active in RCC pathogenesis seemed to amplify the anti-tumour effect of any one monotherapy. The phase III trial of pembrolizumab plus axitinib versus sunitinib noted a markedly improved 12-month overall survival (OS), progression-free survival (PFS) and ORR and led to FDA approval of the combination in March 2019 as initial therapy across risk groups and regardless of PD-L1 expression [3]. Approval of the avelumab plus axitinib combination soon followed in May 2019 based on phase III data showing significantly improved PFS over that with sunitinib in patients with PD-L1 positive tumours; this difference persisted across the intention-to-treat population regardless of PD-L1 status, albeit to a lesser degree [4].

Wang, et al. undertook a comprehensive network meta-analysis of frontline therapies in mRCC including a total of 25 RCTs encompassing 23 different treatments and 13,010 patients. By ranking treatments by both efficacy and safety profile, they appropriately recognized that quality of life is as important as duration of life in metastatic disease. Additionally, their use of OS as the primary endpoint recognizes this as the gold standard of efficacy and the most patient-important endpoint available in clinical research. The authors approached their own use of a network meta-analysis with caution and performed sensitivity analyses in which they excluded studies at higher risk for performance or detection bias, studies that included non-clear cell RCC (nccRCC) histologies and phase II (rather than III) trials, ultimately reinforcing their original conclusions. Overall, the authors provide very practical data for providers who treat patients with mRCC.

For any network meta-analysis, a few questions must be addressed before the findings can be clinically applied. First, mRCC is a heterogeneous disease in which individual patient-level factors such as tumour heterogeneity, performance status, PD-L1 status and risk category matter greatly in determining treatment response. Incorporation of these factors into the network meta-analysis of Wang, et al. was not possible. In addition, the primary endpoints of PFS and OS require different power calculations and direct comparison of OS between studies in which OS is a primary versus a secondary endpoint presents methodological challenges. A prime example of this challenge is the analysis of the CABOSUN trial, a phase II trial in which PFS was the primary endpoint, only intermediate- and high-risk patients were enrolled, and ultimately cabozantinib improved upon sunitinib by measure of PFS [5]. Within the meta-analysis, these differences in patient population and primary endpoint compared to other trials may at least partially account for the discrepancy noted in the relative efficacy of cabozantinib in prolonging PFS compared to OS. The authors’ acknowledgement of these limitations reflects the rigour of their investigation and also the need for additional phase III trials with non-sunitinib comparator arms. Given the recent approval of multiple targeted therapy plus immunotherapy combinations, a method of determining which disease subsets are most likely to respond to immunotherapy versus angiogenesis inhibition is essential.

One potential solution to this therapeutic quandary lies in the quest for a biomarker capable of aligning patient selection with the optimal mechanism of treatment. While PD-L1 expression is known to play a role in responsiveness to CPIs, those without PD-L1 expression still derive benefit from these therapies. Tumour mutational burden (TMB) is another potential biomarker of response to CPIs that has not been highly relevant in mRCC. Recently, tumour gene expression signatures found highly angiogenic tumours to be more likely to respond to sunitinib than the immunotherapy/anti-VEGF combinations and tumours with pre-existing immunity, as evidenced by high T-effector presence and...
function, more likely to respond to combination therapy over sunitinib [6,7]. These studies represent an initial attempt to identify a molecular signature capable of assisting with treatment decisions in the era of immunotherapy and anti-angiogenesis combinations.

Wang, et al. established an important benchmark in the present-day management of mRCC, a landscape that is only poised to increase in complexity in the near future. There are currently several ongoing phase III clinical trials in frontline treatment of mRCC, including cabozantinib plus nivolumab versus sunitinib (NCT03141177), ipilimumab plus nivolumab with or without cabozantinib (NCT03937219), lenvatinib plus either pembrolizumab or everolimus versus sunitinib (NCT02811861), and NKTR-214, a novel IL2 pathway agonist, plus nivolumab versus either sunitinib or cabozantinib (NCT03729245). Another important trial is investigating induction with nivolumab plus ipilimumab followed by maintenance with either nivolumab or nivolumab plus cabozantinib and promises novel insights into response-predictive biomarkers (NCT03793166). Having multiple efficacious first-line treatments is ultimately a welcome problem and Wang, et al. have laid the groundwork for our next charge of personalizing frontline therapy choice and the relatively untouched realm of ideal treatment sequence for the individual patient.

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