Third-line treatment in metastatic renal cell carcinoma and bone metastases

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The treatment of metastatic renal cell carcinoma (mRCC) has advanced to the point that we now have studies routinely examining third-line targeted therapies. Iacovelli and colleagues have published an important analysis examining the role of bone metastases in prognosis and prediction of efficacy in the third-line setting.[1] This work confirms previous publications that bone metastases in mRCC are associated with a poorer overall survival.[2] However, the search for predictive markers that can help determine which agent is more efficacious for a particular patient remains elusive. As seen in this publication, the presence of bone metastases does not change the efficacy of targeted therapy.

This work specifically studied third-line therapy outcomes. It may be reasonable to believe that the bone metastases results would be applicable across all lines of therapy, although this should be studied in greater depth. The hypothesis-generating result that everolimus seems to outperform sorafenib in the third-line setting should be tempered with the fact that this is a retrospective analysis, as pointed out by the authors. There are obvious differences between the two groups especially in terms of previous targeted therapy which are not delineated in this paper. Finally, because axitinib is relatively new and not included in these studies, it is unknown how this newer VEGF inhibitor would compare.[1]

Bone metastases are often difficult to treat in mRCC. Their response to targeted therapy is less satisfactory compared to other sites, such as lung metastases. The customized use of localized therapies, such as stereotactic radiosurgery, radiation or even surgery, may provide palliative benefit to these patients if the targeted therapies produce suboptimal results.

Although outside the scope of this study, questions about sequencing therapies in the setting of first-, second-, third-line and beyond come to mind. Newer agents, such as the VEGF/Met inhibitor cabozantinib[3] or the next-generation immunotherapy PD-1 inhibitor nivolumab, have arisen.[4] Perhaps now sufficient differences in mechanism of action may allow sequencing therapy to produce longer overall survivals rather than our current state of juggling anti-angiogenesis inhibitors. Additionally, these new targets would be fertile ground to find predictive biomarkers of efficacy.

In the rapidly evolving armamentarium of therapies against mRCC, we will need to constantly readdress studies like this in prognosis and the challenging search for predictive biomarkers. This study is helpful in that it delineates expectations for third-line therapy outcomes and I would expect that with the approval and reimbursement of newer agents that we would see outcomes continue to improve for our patients.

Competing interests: Dr. Heng declares no competing financial or personal interests.

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