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COMMENTARY

Metastatic RCC: Moving Towards a Chronic Disease

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The article by Posadas and Figlin on systemic therapy in advanced renal cell carcinoma (RCC) provides a very interesting and comprehensive review of our current knowledge concerning the treatment of RCC. As stated by the authors, this field has changed dramatically in the past 6 years, with the approval of six new drugs and at least two additional approvals coming in the very near future. However, after reading this article, readers might be somewhat disappointed by the lack of clear-cut recommendations regarding how they should treat specific patients presenting at their clinic.

One of the "advancing paradigms" referred to by the title of the review derives principally from the fact that approval has been provided, drug after drug—without, however, any attempt to prioritize the drugs. A good example of such a paradigm can be found in the recommendation for first-line treatment of clear-cell carcinoma, for which three regimens have been approved with the same level of evidence (sunitinib [Sutent], bevacizumab(Drug information on bevacizumab) [Avastin] + interferon, and pazopanib [Votrient]). Head-to-head trials will certainly help define priorities to some degree, although guidelines will probably keep all the regimens as possible options in the future. However, one must wonder whether, if axitinib (Inlyta) and tivozanib are approved as first-line treatment when the data from ongoing phase III trials are presented, the other agents should remain as options.

Another important paradigm in RCC management derives from the lack of biomarkers for this disease. Although targeted therapy is currently the standard of care in RCC treatment, none of the targets have been shown to accurately predict the efficacy of the drugs we are using. This finding underlines the urgent need for validated biomarkers that can help physicians make the best choices for their patients. Similarly, although mechanisms of resistance to tyrosine kinase inhibitors (TKIs) are emerging—eg, production of cytokines such as interleukin (IL)-8, fibroblast growth factor (FGF), angiopoietin—many questions remain as to whether using drugs that block production of these cytokines (for example, dovitinib, which is currently being studied in vascular endothelial growth factor [VEGF]-refractory patients) will be able to overcome these resistance phenomena.

The authors have tried to define an algorithm for the management of advanced RCC in their Figure. Here there are some differences between the United States and Europe. In Europe, we feel that there is no evidence that non–clear-cell histology will benefit from temsirolimus (Torisel), and we still consider TKIs as the standard of care in this subgroup. Similarly, European RCC experts no longer use high-dose

IL-2, based on the finding that no characteristics facilitate determination of which patients are suitable for this toxic treatment. Obviously, if new data from the SELECT trial reveal new information, this position will be quickly changed.

An important issue raised by the authors concerns the choice of subsequent treatment after first-line treatment has failed, which unfortunately is the case in the vast majority of patients. Two large phase III trials have positioned two new agents as standard-of-care in this setting, everolimus (Afinitor) and axitinib (which was recently approved by the US Food & Drug Administration [FDA] and is currently under examination by the European Medicines Agency [EMEA]). In order to provide help with clinical decisionmaking, a head-to-head study comparing those two drugs will be necessary, instead of indirect and biased intratrial comparisons. However, the field is moving so fast that new treatment options might make such a trial rapidly obsolete.

In fact, many new pathways are being explored, and the preliminary data are very exciting. Dovitinib, an FGF inhibitor, has impressive activity in heavily pretreated patients. Dual inhibition of cMET and VEGF, provided by drugs such as foretinib or cabozantinib, also looks very attractive. Similarly, the more potent inhibition of the Pi3K/Akt/mammalian target of rapamycin (mTOR) pathway is thought to be more active than that of the first-generation mTOR inhibitors (temsirolimus, everolimus). Whether this is confirmed by ongoing trials may change the landscape dramatically.

Finally, targeted immunotherapy has provided new hope in the management of RCC. CTLA-4 inhibitors, as well as inhibitors of PD-1 and PDL-1, have very promising activity, and the prospect of testing these drugs in early-stage disease appears very exciting. In addition, because of their different mechanism of action, these drugs might be safely combined with current drugs, thereby providing a major step forward toward the cure of metastatic disease. And this is very good news. Metastatic RCC now has a much longer overall survival, and the possibility of rendering this disease chronic—and some day curable—is approaching.

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