Novel Therapies in the Honeymoon Period

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The elegant and thoughtful review of current management of renal cell carcinoma, by Feldman and Motzer,[1] indicates that there has been clear and defined progress in the management of this frustrating disease. Our limited understanding of the biology of the immune response in renal carcinoma has led to the use of the interferons and varying doses of interleukin-2 (Proleukin), occasionally and inconsistently achieving spectacular, durable responses, but often at the cost of significant toxicity.

Keys to Success
As Feldman and Motzer discuss, surgical debulking clearly has a role in this setting,[3,4] whether the effect is due to specific bulk reduction of tumor load or an implicit immunologic benefit from the removal of tumor that constitutes a target of the immune response to renal carcinoma. In most circumstances, the impact is modest, although many oncologists currently see surgical removal of the primary tumor as one of the keys to success.
With the advent of targeted therapies, including the tyrosine kinase inhibitors and agents that interfere with mammalian targets of rapamycin (mTOR), a panoply of exciting treatment options is afforded, and patients are experiencing sustained tumor remissions. At present, as is so characteristic of the early development of novel compounds, we are in the honeymoon period, and these drugs are seen as much less toxic and much more exciting than our so-called standards. Time and more clinical experience will tell us whether this is an accurate construct.

Multiple Applications
As described by Feldman and Motzer, these agents have many different potential applications, as adjuvant treatment after resection of the primary, in combination with each other, with conventional drugs, or with various immune modulators. The early studies of sorafenib (Nexavar) have been characterized by the productive application of randomized discontinuation approaches, focusing the drug on specific responding populations of patients. While this strategy has surely worked to our benefit, it remains a trap for young players—that is, the molecular pathways involved are both intuitive and counterintuitive, and there is the potential for unexpected downstream effects and interactions of these drugs.
We need to be creative in developing and implementing novel treatment strategies and combination approaches, while trying to maximize our use of relatively limited patient resources. Nevertheless, it is important to remember that stringent economy of trial design may lead us to miss the true activity of some of these compounds and combinations,[5] and we need to ensure that our studies are powered to tell us the truth. Even with a proliferation of promising new compounds and early evidence of anticancer activity, we need to encourage ourselves and our colleagues to recruit patients to clinical trials until cure is the expected result for advanced renal cancer.

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References:
1. Feldman D, Motzer R: Novel targets and therapies for metastatic renal cell carcinoma. Oncology


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