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**Editorial Comment on: Vaccine Therapy in Patients with Renal Cell Carcinoma**

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Immune-stimulating approaches have resulted in low but reproducible response rates in patients with metastatic renal cell carcinoma (RCC). A key feature of these responses is that they are frequently durable, providing a rare chance of cure in small subsets of patients, which led to the approval of high-dose interleukin 2 (IL-2) by the US Food and Drug Administration. Newer generations of immune-stimulating and vaccine platforms have been tested to avoid the high toxicity of IL-2.
In RCC, a limited number of tumor associated antigens have been identified, which has led to the testing of cell-based tumor vaccines. Approaches have included gene-modified tumor cells and dendritic cell-based vaccines [1]. Most of these approaches, however, failed to demonstrate significant efficacy in randomized phase 3 trials. The single exception was Reniale, a patient-specific vaccine using lysates from autologous tumors cells extracted at the time of surgery. Although promising results were reported with Reniale, questions arose regarding the study design [2]. There are plans to conduct an international phase 3 trial to confirm these results, which will hopefully lead to regulatory approval for the product.

As Van Poppel et al [3] describe in their review article, there have been a number of phase 3 clinical trial failures in the field of RCC. What explains these failures [4,5]?

Some vaccines (eg, Oncophage) may have low potency to induce specific T-cell responses, resulting in controlling patients with only small-volume disease. The pivotal clinical trial of Oncophage showed improvement in the unplanned analysis of earlier stage patients but not in the overall patient population.

Other vaccines (like Trovax) use single-cancer antigens that may facilitate treatment escape through downregulation or total expression loss. Additionally, in the Trovax trial, problems in the design, like the use of adjuvant alone in the control arm, could also have skewed the statistical power.

Finally, the development decisions of a vaccine program need to be based on clinical data, not just on immune response (eg, with Vitespen, for which rare objective regressions of metastatic disease were seen). Immune responses have not been predictive of clinical benefit. The rare vaccines that do generate brisk B-cell or T-cell responses, for example, apparently do not induce the correct effector functions to reject tumors or to overcome immunosuppression.

As stated by Van Poppel et al [3], the success of clinical effectiveness in selected populations combined with more potent vaccines with novel adjuvants and strategies aimed at circumventing tumor-associated immunosuppression [4] may improve the efficacy of tumor vaccines and cellular immunotherapy so that they live up to their promise.

References


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The range of options available for treating advanced renal cell carcinoma (RCC) has expanded tremendously in the last several years. It was not that long ago that the only options available were immunomodulatory approaches such as high dose interleukin 2 or interferon-α. The menu has now expanded with a variety of targeted therapies, including tyrosine kinase inhibitors such as sunitinib and sorafenib, mammalian target of rapamycin (mTOR) inhibitors such as temsirolimus, and vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab. With all of these options, one might legitimately ask, why bring up another treatment approach such as vaccine therapy?

The truth is that neither the older immunomodulatory approaches nor the more recent targeted therapies frequently cure patients with advanced RCC. To be sure, the targeted therapies are a major advance and have changed the way this disease is managed, but there is still plenty of room for