Immunotherapy in Renal Cell Carcinoma

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Very little has changed in the management of advanced renal cell carcinoma since the approval of interleukin-2 (IL-2, aldesleukin [Proleukin]) in 1992 by the FDA for the systemic treatment of this disease. Dr. Bukowski succinctly reviews the current treatment options for this patient population and also alludes to the variable natural history of patients with metastatic renal cell carcinoma. Since the initial studies documenting the activity and toxicity of the high-dose intravenous bolus regimen of IL-2, there have been numerous reports, described by Dr. Bukowski, of low-dose IL-2 regimens administered either alone or together with interferon-alfa (Intron A, Roferon-A) and/or fluorouracil. Most of these low-dose outpatient regimens have reported results equivalent to those seen with the high-dose regimen with regard to overall response rates.

High- vs Low-Dose IL-2

The benefit of the low-dose regimens has been less severe toxicity than has been seen with the high-dose regimen, which makes the low-dose regimens applicable to a broader patient population with metastatic renal cell carcinoma. The vast majority of these regimens, however, are based on the administration of IL-2 over extended periods. Thus, while the intensity of toxicity is lower with the low-dose regimens than with high-dose IL-2 therapy, the duration of side effects (ie, fatigue, nausea, diarrhea, and anorexia) is much longer.

One of the advantages of the high-dose regimen over the low-dose single or combination regimens has been the documented long response duration of the former. With long-term follow-up of a patient database of 255 patients treated with high-dose IL-2 (information on file with the FDA), Chiron Corporation documented a 7% complete response rate and an 8% partial response rate, with > 70% of complete responders and approximately 20% of partial responders showing no disease progression beyond 5 years. Long-term remission durations of this magnitude have not been reported with other IL-2 regimens.

We agree with Dr. Bukowski that randomized trials comparing the high-dose regimen with low-dose regimens are needed. In the interim, preliminary results of a randomized three-arm IL-2 trial conducted by the Surgery Branch of the National Cancer Institute (NCI) have been reported at a symposium held in Washington, DC, in 1996. The study randomized patients between high-dose intravenous (720,000 IU/kg every 8 hours, low-dose intravenous (72,000 IU/kg every 8 hours), and low-dose subcutaneous IL-2 (120,000 IU/d for 5 days each week). That study enrolled 260 patients and demonstrated an advantage for the high-dose bolus regimen with respect to response rate, response duration, and overall survival.[1]

We also await the results of the Cytokine Working Group’s multi-institution trial comparing high-dose IL-2 with a low-dose outpatient regimen. For patients who do not have access to this randomized, phase III trial, many centers are performing phase II trials that are also attempting to answer important questions.

Newer Treatment Strategies

Newer strategies for the treatment of advanced renal cell carcinoma are coming from basic research into the molecular biology of this disease and into host/tumor immunologic interactions. Various vaccination techniques are being evaluated in metastatic melanoma[another tumor that responds to immunologically based therapeutic approaches. However, while there are multiple tumor-associated antigens available for developing vaccines in melanoma, we have not been as successful in identifying renal cell carcinoma[associated antigens to use as targets. Recently, the G250 antigen, a renal cell carcinoma[specific antigen, has been identified and cloned.[2] This antigen is expressed on all clear cell, and the majority of non-clear cell, renal cell carcinomas. Ongoing studies are evaluating the potential use of this antigen in the immunotherapy
of renal cell carcinoma. Another potential antigen to target in the immunotherapy of renal cell carcinoma is the HER-2/neu protein, which has been reported to be overexpressed in renal cell carcinoma and may be a target for cytotoxic T-cells.[3]

As newer methods are developed in identifying tumor-associated antigens, it is hoped that other renal cell carcinoma antigens will be isolated. We have taken the approach of using whole autologous tumor cells admixed with bacillus Calmette-Guérin (BCG) as a vaccine to immunize patients with renal cell carcinoma. The vaccine is used to prime draining lymph nodes, which are subsequently harvested for ex vivo activation and expansion of T-cells used for adoptive therapy. We have been able to generate both CD4+ and CD8+ T-cells reactive to autologous tumor cells, which underscores the presence of various target antigens on renal cell carcinomas. Better understanding of the interaction between host and tumor may lead to improved treatment strategies for renal cell carcinoma, as well as other tumor types. Dr. Bukowski’s group has been in the forefront of attempting to identify T-cell defects that occur in patients with renal cell carcinoma. Others have been evaluating factors that may be important in immune suppression, such as interleukin-10 (IL-10) and Fasligand. These proteins may be expressed at the interface between tumor and host response, resulting in local immune suppression. Some or all of these mechanisms may be operative in the majority of patients who do not respond to immunologically based therapies.

For the future, there are multiple avenues for continued preclinical and clinical investigations with antiangiogenic agents, novel chemotherapeutic agents with new molecularly defined targets, and gene transfer approaches. An ongoing multi-institution study is evaluating the intratumoral delivery of liposomes complexed with the gene encoding IL-2 in patients with metastatic renal cell cancer. Patients with renal cell carcinoma should be encouraged to participate in ongoing clinical investigations.

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