Immune Therapy for Kidney Cancer: A Second Dawn?

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Agents targeting the immune system have been a historical standard of care in metastatic renal cell carcinoma (RCC), but have largely been supplanted by newer targeted therapy. Recent insights into the regulation of an anti-tumor immune response has led to the development of agents that can activate immune responses primarily within the tumor, enabling the possibility of achieving durable tumor response in the absence of significant systemic toxicity. In addition, a better understanding of tumor immunology has raised the potential of developing predictive biomarkers of response to immunotherapy. Novel approaches including inhibition of immune checkpoints has entered clinical testing in RCC.
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Although immunotherapy was once considered the standard of care for patients with metastatic renal cell cancer (RCC), the advent of therapies that target angiogenesis and signal transduction pathways produce significant clinical benefits and thus have led to a substantial reduction in its use.[1–4] The application of vascular endothelial group factor (VEGF) and molecular target of rapamycin (mTOR) pathway inhibitors has led to improved progression-free survival and overall survival and less toxicity for the general population of patients with metastatic RCC relative to immunotherapy, restricting the use of immunotherapy (particularly high-dose interleukin-2 [IL-2]) to highly select patients treated at highly selected centers with interest and experience in its administration.[5–7] Recent insights into how the immune response to a tumor is regulated has led to the development of agents that can activate immune responses primarily within the tumor, enabling the possibility of achieving durable tumor response in the absence of significant systemic toxicity.[8–10] In addition, better understanding of tumor immunology has raised the potential of developing predictive biomarkers of response to immunotherapy. These new agents and scientific developments together with the increasing awareness of the limitations of the antiangiogenic and molecularly targeted therapies have prompted a resurgence of interest in cancer immunotherapy. This review describes how improvements in patient selection, combination therapy, and investigational agents might expand and better define the role of immunotherapy in patients with metastatic RCC.

CYTOKINE THERAPY

Although a number of cytokines have shown antitumor activity in RCC, the most consistent results have been reported with interferon-alfa (IFN-α) and IL-2. Although IFN-α has produced modest benefits in unselected patients, a meta-analysis of randomized clinical trials revealed a 3-month survival benefit with manageable toxic effects when compared with non–IFN-α control arms.[11–15] In the absence of other effective and readily applicable treatments, IFN-α became a de facto standard of care worldwide, justifying its use as the control arm for registrational randomized trials with targeted therapies that are described elsewhere in this issue of *Seminars in Oncology*.[2–4] The results of these investigations have, in general, established the superiority of targeted agents in treatment-naïve patients with metastatic RCC, thereby limiting the use of IFN-α as a single agent in this setting.

In contrast to the results seen with molecularly targeted therapies (eg, pazopanib, sunitinib), which

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Table 1. Select Randomized Trials of Cytokine Therapy in Metastatic Renal Cell Cancer

Trial	Treatment Regimens	N	Response Rate (%)	Durable Complete Response (%)	Overall Survival (mo)*
French Immunotherapy Group[16]	CIV IL-2	138	6.5	1	12
	LD SC IFN-α	147	7.5	2	13
	CIV IL-2 + IFN-α	140	18.6	5	17
	MPA	123	2.5	1	14.9
French Immunotherapy Group[19]	LD SC IFN-α	122	4.4	3	15.2
	LD SC IL-2	125	4.1	0	15.3
	SC IL-2 + IFN	122	10.9	0	16.8
National Cancer Institute Surgery Branch[17]	HD IV IL-2	156	21	8	NR
	LD IV IL-2	150	13	3	NR
	HD IV IL-2	95	23	7	17.5
Cytokine Working Group[18]	LD SC IL-2/ IFN-α	91	10	NR	13
	HD IV IL-2	95	23	NR	17.5

Abbreviations: CIV, continuous intravenous infusion; CR, complete response; HD, high dose; IFN-α, interferon alfa; IL-2, interleukin-2; IV, intravenous; LD, low dose; MPA, medroxyprogesterone acetate; NR, not reported; RR, response rate; SC, subcutaneous.

*The overall survival difference was not statistically significant in all cases.

lead to tumor shrinkage in most treated patients but do not reliably produce either complete responses or sustained tumor remissions when therapy is discontinued, the administration of high-dose bolus IL-2 has consistently produced durable off treatment complete and partial responses in a small percentage of patients with advanced RCC (Table 1).[16–19] This durable benefit, while highly desirable, must be balanced against the nearly universal substantial toxicity of IL-2 and the inability to identify the patients most likely benefit. Consequently, the application of high-dose IL-2 was increasingly limited to highly motivated and variably selected patients treated at specialized centers.[5–7]

Efforts to identify predictors of response to high-dose IL-2 focused on retrospective evaluation of treatment datasets. These analyses led to the proposal of a variety of potential feature favoring response to IL-2, including clear cell histology, prior nephrectomy, performance status 0 or 1, absence of nodal status, and carbonic anhydrase IX (CAIX) staining.[18,20–24]

The Cytokine Working Group (CWG) conducted the high-dose IL-2 "SELECT" trial to determine, in a prospective fashion, if these various proposed predictive models could identify a group of patients with advanced RCC who are significantly more likely to respond to high-dose IL-2–based therapy (good risk) than a historical, unselected patient population.[24] The primary model used for the statistical design of this study combined tumor CAIX expression and certain histologic features of the tumor,[24] although patients were eligible for enrollment regardless of whether they satisfied the good-risk criteria of this model. The clinical results of this trial revealed a response rate (25%) that was significantly higher that the historical experience with high-dose IL-2.[25] More than 40% of patients exhibited tumor shrinkage and median overall survival for the population exceeded 36 months, suggesting that in the era of molecularly targeted therapy the efficacy of high-dose IL-2 might be significantly better than reported in the registration studies. Hypotheses supporting this higher efficacy included (1) the routine restriction of treatment to patients with largely clear cell RCC who had performance status of 0 or 1 and had undergone prior nephrectomy, (2) the availability of other therapies limiting the referral of patients for IL-2 to those who the referring oncologist deemed for whatever reason to be more likely to benefit, and (3) the application and maintained efficacy of VEGF and mTOR pathway inhibitors in those patients whose disease progressed after high-dose IL-2. However, despite these encouraging clinical results, analysis of proposed tumor predictive biomarkers was unable to confirm the principal hypothesis generated in the retrospective studies. This finding both called into question the value of such retrospective studies and left clinicians without a means of further defining which patients should receive high-dose IL-2. Efforts to confirm other proposed biomarkers (eg, CAIX single nucleotide polymorphisms [SNPs], PDL-1 expression) are ongoing to understand tumor and host factors that predict for remissions following IL-2 therapy.[26] It is still hoped that an improved model for IL-2 patient selection will likely emerge from these efforts although any novel finding might require prospective of at least independent validation before it could be comfortably applied to clinical decision making. More likely, lessons from this work could