

Role of Immunotherapy for Renal Cell Cancer in 2011

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Key Words

Renal cell cancer, immunotherapy, interleukin, tumor immunity

Abstract

High-dose interleukin-2 (IL-2) and interferon were the most commonly administered therapies before the recent introduction of targeted agents, including vascular endothelial growth factor and mammalian target of rapamycin pathway inhibitors. Although the new agents result in a progression-free survival benefit, high-dose IL-2 remains the only agent with proven efficacy in producing durable complete and partial responses in patients with metastatic renal cell carcinoma (RCC). Furthermore, although the use of single-agent interferon has decreased significantly since the introduction of targeted therapy, it remains in the frontline setting in combination with bevacizumab as a result of 2 large phase III trials. Lastly, improved understanding of immune regulation has led to the advancement of targeted immunotherapy using immune checkpoint inhibitors that have shown promising activity and are moving forward in clinical development. This article focuses on the current status of immunotherapy in the management of metastatic RCC. (*JNCCN* 2011;9:1011–1018)

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Although the new agents result in a progression-free survival benefit, high-dose IL-2 remains the only agent with proven efficacy in producing durable complete and partial responses in patients with metastatic renal cell carcinoma (RCC). Furthermore, although the use of single-agent interferon has decreased significantly since the introduction of targeted therapy, it remains in the frontline setting in combination with bevacizumab as a result of 2 large phase III trials.¹ Lastly, improved understanding of immune regulation has led to the advancement of targeted immunotherapy using immune checkpoint inhibitors that have shown promising activity and are moving forward in clinical development. This article focuses on the current status of immunotherapy in the management of metastatic RCC.

The incidence of RCC is on the rise, with an annual incidence of 58,000 cases as of 2010.² RCC comprises a group of tumors arising from the epithelium of the kidney. The predominant types of kidney cancer include clear cell RCC (75%), papillary RCC (15%), chromophobe type (5%), and oncocytic type tumors. Furthermore, clear cell RCC, the most common and extensively studied histologic subtype, is characterized in most cases by distinctive features, including Von Hippel-Lindau (VHL) genetic and epigenetic silencing, resulting in accumulation of hypoxia-inducible factor, production of various proangiogenic growth factors, dependence on new blood vessel formation, and, finally, host immune dysfunction. In localized disease, surgery remains the preferred therapeutic modality for cure. In the metastatic setting, however, systemic treatment approaches are multifaceted and include immunotherapeutic approaches, such as IL-2, and signal transduction inhibitors, such as VEGF-targeted therapies and mTOR inhibitors.^{3–11}

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Role of Immunotherapy in RCC

The clinical application of immunotherapy became widely accepted after the significance of immune dysfunction that occurs in RCC became understood. Prior reports of spontaneous regression of small metastases after the removal of primary tumors have long suggested that immune-mediated approaches may be feasible. As documented by many studies thereafter, RCC is a unique malignancy in that it impairs tumor immunity through indirectly effecting the proliferation of T-regulatory (T_{reg}) cells and myeloid-derived suppressor cells, and shifting the Th-1/Th-2 bias toward a proinflammatory status.^{12–14} Significant factors that lead to impaired immunity include the expression of B7-H1 and B7-H4 on the tumors, which, upon binding their receptors, act as negative regulators of T-cell-mediated immunity.^{15,16} The following section discusses the data on high-dose IL-2, interferon, and other immunomodulatory approaches currently being studied.

High-Dose IL-2

For many investigators, high-dose IL-2 remains a valuable option for select patients with metastatic RCC because of its ability to produce durable responses. The FDA approved high-dose IL-2 in 1992 for use in metastatic RCC after several clinical trials showed durable complete responses in up to 7% of patients. No trial has been conducted to show a survival advantage of IL-2, but the durability of patient response has been recognized and has warranted continued use of high-dose IL-2, especially in patients with low-volume disease, good performance status (ECOG 0 or 1 or Karnofsky performance status 70–100), and lung/mediastinal-only disease.¹⁷ It is administered as an infusion of 600,000 IU/kg every 8 hours over 15 minutes on days 1 through 5 and 15 through 19 every cycle; 2 to 3 cycles are usually considered for patients who experience response. One cycle allows no more than 28 doses (or 14 doses in 5 consecutive days). The challenges of therapy include expertise in administering the treatments and close monitoring of the cardiopulmonary status.¹⁸

Various other agents have been used for stimulating the tumor immunity. However, the most consistent results have been produced by high-dose IL-2, with the most recent reports noting response rates nearing 28%.⁴ Patients who had experienced response (complete or partial) to high-dose IL-2 had

a median duration of response of approximately 19 months.³ Durable complete responses were noted in up to 7% of patients with metastatic RCC after the use of high-dose IL-2, and these patients were progression-free at a median of 30 months.^{3,19}

Furthermore, the clinical behavior of RCC varies with histology and subtypes. Sarcomatoid dedifferentiation is identified as an aggressive phenotype that portends poorer outcome. A small retrospective study conducted by Cangiano et al.²⁰ showed that treatment with high-dose IL-2 in sarcomatoid patients was associated with improved survival compared with surgery alone or other types of immunotherapy ($P = .025$). In contrast, a retrospective study by Upton et al.²¹ involving papillary RCC and granular features showed lack of benefit from high-dose IL-2 in these subsets of patients.

The most recent study involving high-density IL-2 was the SELECT trial, which was a multicenter, nonrandomized, phase II study that attempted to improve its therapeutic index. The study involved 120 patients with predominantly clear cell RCC (96%) and hypothesized that the response rate to high-dose IL-2 in a preselected population with good pathologic predictive features ($> 50\%$ alveolar features and no papillary or granular features) would be superior to that of a historical unselected population.^{21,22} Most patients had intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk factors (94%) or an intermediate or good University of California, Los Angeles (UCLA) Survival After Nephrectomy and Immunotherapy (SANI) score, and 99% underwent prior nephrectomy.²³ IL-2 was administered in a standard fashion. The toxicity profile was as expected, including 2 treatment-related deaths. This study reported a response rate of 28% (22% partial and 6% complete; Table 1), with a median progression-free survival of 4.2 months (Figure 1). Surprisingly, response to IL-2 was not associated with any pretreatment clinical factors nor was it seen in patients with non-clear cell histology and high UCLA SANI score. Additional analyses from this trial are ongoing in search of biomarker of response to IL-2 that can be validated in subsequent studies.

The therapeutic armamentarium for metastatic RCC considerably expanded in the past several years with the introduction of targeted agents.^{5,6,8–10,24,25} Currently, however, definitive recommendations on the optimal sequence of administering high-dose

Table 1 Response by Baseline Characteristics

All Patients (n = 120)	RR (95% CI) 25% (18%–34%)	P Value .0014
Tumor Type		
Clear cell (n = 115)	26% (18%–35%)	.33
Non-clear cell (n = 5)	0% (0%–52%)	
MSKCC Risk Group		
Favorable (n = 21)	23% (7%–44%)	.89
Intermediate (n = 81)	25% (16%–36%)	
Poor (n = 18)	31% (9%–61%)	
UCLA Risk Group		
Low (n = 10)	20% (3%–56%)	.27
Intermediate (n = 101)	27% (19%–37%)	
High (n = 8)	0% (0%–37%)	

Abbreviations: MSKCC, Memorial Sloan-Kettering Cancer Center; RR, relative risk; UCLA, University of California, Los Angeles.

Courtesy of David McDermott, MD, Boston, MA. Presented at the 2010 ASCO Annual Meeting; June 4–8, 2010; Chicago, Illinois.

IL-2 and various signal transduction inhibitors remain elusive, mostly because of the lack of available data. Reports have shown that patients who receive IL-2 after anti-VEGF therapies experience increased toxicities, particularly cardiac-related.²⁶ Alternatively, targeted agents after cytokine therapy have been shown to be safe. The TARGET trial of sorafenib, which was conducted in patients who experienced

progression after first-line cytokines, including interferon and IL-2, reported no major increased toxicity in patients who had received prior IL-2 (42%).⁵ Furthermore, sunitinib was found to be similarly efficacious and safe in phase II studies conducted in patients with cytokine-refractory RCC.^{27,28} Similarly, pazopanib was also determined to be safe in a large phase III trial that included patients with RCC who were treatment-naïve and those who were cytokine-refractory.²⁵ Based on these results, and because increased toxicities have been reported in patients treated with IL-2 after exposure to VEGF tyrosine kinase inhibitors, it may be worthwhile to consider IL-2 as a first-line therapy in patients who meet the clinical and pathologic criteria for this treatment.

Lastly, preclinical and clinical studies are ongoing to enhance the immune response mediated by IL-2. For example, one combination strategy is to decrease the inhibitor effects of T_{regs} with the use of histone deacetylase inhibitors in conjunction with high-dose IL-2 (ClinicalTrials.gov identifier: NCT01038778).^{29–31}

Interferon

Historically, interferon was the standard frontline option in the treatment of metastatic RCC. Interferon as a single agent had been associated with a small proportion of patients with RCC experiencing clinical benefit, with median survival reaching 13 months.^{32–35} In a retrospective analysis of 460 patients from various trials who received interferon- α , Motzer et al.²⁸ observed that the median time to progression was 4.7 months and the median overall survival was 13 months. This study was able to identify the risk factors associated with poor outcome (MSKCC risk factors), which are widely used today for prognostication purposes in patient counseling and clinical trial design.³³ As the de facto standard frontline therapy, interferon logically became the default standard for comparison in first-line trials that led to the approval of 3 targeted agents in RCC,^{6,9,24} including the phase III trials of sunitinib and temsirolimus. Because of the improved progression-free survival seen in the experimental arms, the use of interferon has been largely replaced by targeted agents in the frontline setting. However, interferon remains part of the armamentarium in the frontline treatment of metastatic RCC in combination with bevacizumab, a regimen that has shown comparable efficacy to a single targeted agent in the frontline set-

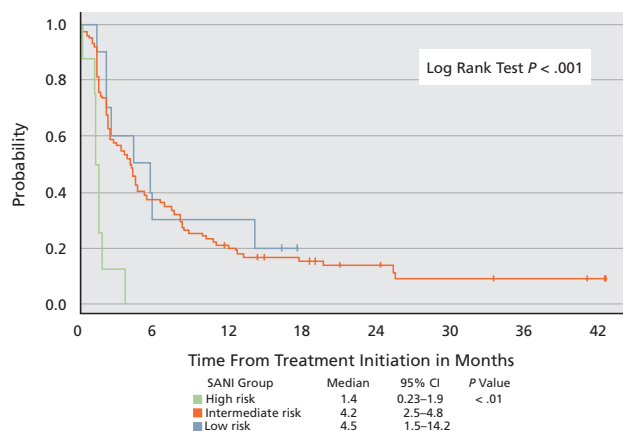


Figure 1 Progression-free survival according to University of California, Los Angeles Survival After Nephrectomy and Immunotherapy (SANI) risk group.

Courtesy of David McDermott, MD, Boston, MA. Presented at the 2010 ASCO Annual Meeting; June 4–8, 2010; Chicago, Illinois.

ting in 2 large phase III trials, and thus was approved as such in both the United States and the European community.^{5,6,8–10,24,25} However, the toxicity profile of the combination was significant, leading to higher drop-out rates in the combination arm.

Experimental Approaches to RCC Immunology

Vaccines and Stem Cell Transplant: The role of reduced-intensity allogeneic stem cell transplant has been explored as an adoptive immunotherapeutic approach in patients with cytokine-refractory metastatic RCC. The most benefit was observed in patients in favorable or intermediate MSKCC risk groups. Various studies showed that transplantation induced a long-term disease-free interval in a small fraction of patients.^{36,37} The development of a graft-versus-tumor effect is thought to be the reason for response among the patients who showed clinical benefit.^{38–40} Various vaccine-based approaches are being explored in RCC in the adjuvant and metastatic settings. The mechanisms explored include vaccine strategies against tumor-associated antigens of RCC and tumor cell lysate along with activated dendritic cells.^{41–44} Several studies are ongoing and results are awaited (ClinicalTrials.gov identifiers: NCT01265368, NCT00862303, NCT00004880).

Other Cytokines and Immunomodulatory Approaches: Other cytokines used include IL-4, IL-6, IL-12, and pegylated forms of interferon, but none has been able to show any clinically meaningful benefit from their application.^{45,46} Two separate trials combining interferon with sorafenib in patients with RCC showed modest improvement in progression-free survival and response rates compared with single agents (ClinicalTrials.gov identifiers: NCT00098618, NCT00101114).³⁸ Even though sunitinib is a signal transduction inhibitor that predominantly targets VEGF signaling, some studies have shown the immunomodulatory effects of this agent in terms of suppressing myeloid-derived suppressor cells and T_{regs}.^{47,48} and warrant further investigation. However, results have been disappointing, with a phase I study in combination with an immune checkpoint inhibitor tremelimumab resulting in significant renal toxicities, which led investigators to recommend against this combination.⁴⁹

Immune Checkpoint Inhibitors: A new area of investigation in cancer immunotherapy involves the specific targeting of regulatory elements of the adaptive immune response. In the past decade, studies

have shown that T cells recognize antigens associated with the major histocompatibility complex as the first signal, but that additional signals via coreceptors are required for optimal T-cell recognition and generation of a potent and long-lasting T-cell immune response (Figure 2). These additional signals for optimal T-cell priming involve agonist coreceptors, such as CD28, 4-1BB, and OX40, and inhibitory coreceptors, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1). Antibodies to these immunomodulatory elements (both the receptors and their ligands) have been developed, and some are moving forward in clinical testing with promising activity, especially in immunogenic tumor models such as melanoma, RCC, breast cancer, and prostate cancer. Ipilimumab is the prototypical antibody directed against CTLA-4, the most extensively studied inhibitory T-cell coreceptor. Ipilimumab has recently been approved for the treatment of patients with metastatic melanoma and studies are ongoing in RCC. PD-1, along with its ligand PD-L1, constitutes another immune inhibitory axis against which abrogating human antibodies (MDX-1106 and MDX-1105, respectively) are undergoing clinical testing.

CTLA-4: CTLA-4 is a member of the CD28:B7 immunoglobulin superfamily and is normally expressed at low levels on the surface of T cells.⁵⁰ CTLA-4 competes with CD28 (immune stimulatory coreceptor) for CD80/CD86 on antigen-presenting cells or tumors, effectively shutting off T-cell receptor signaling.⁵¹ In vitro and in vivo, T cells lacking CTLA-4 have been shown to exhibit high rates of proliferation and an activated phenotype, providing a therapeutic rationale in tumor models such as melanoma and RCC that result in host immune dysfunction partly by inhibition of T-cell activation and proliferation.⁵²

Ipilimumab is a fully humanized monoclonal antibody against CTLA-4 that showed promising activity in several phase II studies in patients who underwent pretreatment for melanoma. This success led to a large phase III study, in which ipilimumab became the first agent to show overall survival benefit in patients with metastatic melanoma, with median survival of 10.1 versus 6.4 months against gp100 vaccine (hazard ratio, 0.66; $P = .003$),⁵³ leading to FDA approval on March 25, 2011. Based on tumor regression seen in patients with melanoma in earlier studies, a phase II study was performed in

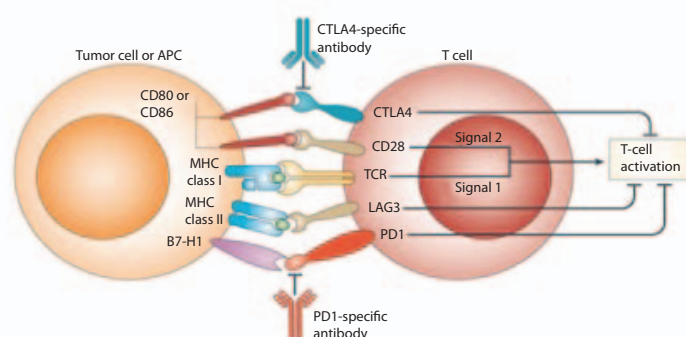


Figure 2 Schematic illustration of antigen-presenting cell/tumor cell and T-cell receptor interaction in T-cell activation.

Abbreviation: APC, antigen-presenting cell; CTLA, cytotoxic T-lymphocyte antigen; PD1, programmed death 1.

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patients with RCC, which showed a response rate of 13% when given at 3 mg/kg every 3 weeks.⁵⁴ As suspected from preclinical studies in which CTLA-4 knockout mice developed a profound lymphoproliferative disorder,⁵⁵ treatment-related toxicities were immune-mediated and occasionally serious in earlier studies, with colitis and hypophysitis being the most common. However, with diligent patient monitoring and appropriate and early institution of corticosteroids and/or immune suppressive agents, such as tumor necrosis factor–blocking agents or mycophenolate, these side effects have proven to be manageable without tempering the therapeutic response.⁵⁶ The anti-CTLA-4 antibody continues to be investigated in RCC in both adults and the pediatric population (ClinicalTrials.gov identifiers: NCT00378482, NCT00556881).

PD-1: PD-1 is another immune checkpoint molecule that is expressed on activated T cells and is involved in regulating the balance between immune activation and tolerance.⁵⁷ It shares homology with CTLA-4 but with distinct immune-inhibitory signals. Engagement of PD-1 by its ligands PD-L1 (B7-H1) or PD-L2 (B7-H2) transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function.⁵⁸ PD-L1, the main ligand of PD-1, was found to be aberrantly expressed on tumors, and its expression of PD-L1 on tumors correlated with the presence of tumor-infiltrating lymphocytes, and with poor clinical outcome for several cancers, including RCC.^{59–62} In preclinical studies, unlike CTLA-4 knockout mice, which showed significant lymphoproliferative disorder and early lethality, PD-1 knockouts showed modest late-onset strain-

and organ-specific autoimmunity.^{63,64} A phase I clinical trial of PD-1 blockade conducted with the fully human monoclonal antibody MDX-1106 in 39 patients with advanced treatment-refractory solid tumors included 1 patient with RCC who experienced a partial response that lasted more than 16 months after a single dose of 10 mg/kg without further therapy.⁶⁵ Furthermore, MDX-1106 was well tolerated, with only 1 patient among the 39 enrolled in the study experiencing a serious adverse event (inflammatory colitis).

An additional phase I study evaluating the safety and efficacy of extended biweekly dosing of MDX-1106 at 1, 3, and 10 mg in patients with advanced solid tumors was conducted and results reported at the 2011 ASCO Genitourinary Cancers Symposium,⁶⁶ with a special focus on RCC. Maximum tolerated dose was not reached. The most frequent drug-related adverse events were fatigue, rash, pruritus, and diarrhea. No relationship was seen between dose and frequency of adverse events. Of the 18 patients on the study, 16 were treated with 10 mg/kg. Median duration of treatment was longer than 7.6 months. The overall response rate was 31% (5/16) and 6 of the 16 patients experienced stable disease that lasted longer than 4 months (37.5%). The median duration of response was greater than 4 months. Of the 2 patients with RCC treated with 1 mg/kg, 1 obtained a complete response for longer than 12 months and 1 had stable disease for longer than 21 months.⁶⁶ However, further studies involving multiple doses will need to be completed to definitively evaluate its safety and efficacy profile. Based on these encouraging results, a phase II dose-rang-

ing study is planned. Lastly, further targeting of the PD-1/PD-L1 axis is under investigation, with anti-PD-L1 antibody (MDX1105-01) currently in the phase I stage in multiple advanced tumors, including RCC (ClinicalTrials.gov identifier: NCT00729664).

Conclusions

Immunogenicity of RCC has allowed unique treatment modalities in the past, including high-dose IL-2 and interferon, which remained the mainstay of systemic management for patients with metastatic RCC for several decades. The recent past has seen reduced use of interferon after the introduction of targeted agents, which have shown progression-free survival benefit compared with interferon in large clinical trial settings. Nevertheless, IL-2 remains the only therapeutic modality to have shown proven durable responses replicated in several large clinical trials. For high-dose IL-2, a high degree of expertise is required in patient selection and administration, which has probably limited its widespread use historically. The appropriate patient population includes individuals with excellent organ function, minimal comorbidity, and good performance status, and IL-2 should be administered in an intensive care type of setting with close evaluation before every dose. This therapy is still recommended and should be performed only at high-volume centers with expertise in choosing the appropriate patient population and managing the untoward toxicities in a systematic fashion.

The future of immunotherapy is exciting and will be determined by the outcome of trials that use newer approaches of immunotherapy, such as MDX-1106 (ClinicalTrials.gov identifiers: NCT00441337, NCT01354431). Other efforts, such as vaccine-based and IL-2 combination approaches, are ongoing and results are anxiously awaited.

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