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IMMUNOTHERAPY IN RENAL CANER:
Update on the Role of IL-2 for Metastatic Kidney Cancer

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Introduction

The ability of some renal tumors to evoke an immune response and the lack of benefit seen with standard chemotherapy and radiation led to the application of immunotherapy for patients with metastatic renal cell carcinoma (RCC).[1-3] In an attempt to reproduce or accentuate this response, various immunotherapeutic strategies have been used, including nonspecific stimulators of the immune system, specific antitumor immunotherapy, adoptive immunotherapy, the induction of a graft-vs-tumor response via allogeneic hematopoietic stem cell transplantation, and the administration of partially purified or recombinant cytokines.[4-14] Although immunotherapy was once the standard of care, the advent of novel therapies that target angiogenesis and signal transduction pathways has produced significant clinical benefits and prompted a reassessment of the role of immunotherapy.[15-18] Recent insights into how the immune response to a tumor is regulated may allow patients to obtain a durable response to immunotherapy without the need for chronic treatment typically required of anti-angionenic and tumor targeted approaches. This review describes how improvements in patient selection, combination therapy, and investigational agents might expand and better define the role of IL-2 in metastatic RCC.

Cytokine therapy

Although a number of cytokines have shown antitumor activity in RCC, the most consistent results have been reported with interleukin 2 (IL-2) and interferon alfa (IFN-α). In contrast to the results seen with VEGFR targeted therapies (eg, sorafenib, sunitinib), which lead to tumor shrinkage in most treated patients but do not produce responses that persist following discontinuation of therapy, the administration of high-dose bolus IL-2 has consistently produced durable responses in a small percentage of patients with advanced RCC.[19-21] However, the substantial toxicity and limited efficacy that are associated with IL-2 have narrowed its application to highly selected patients treated at specialized centers.[22,23] Although IFN-α has produced modest benefits in unselected patients, randomized clinical trials have revealed a small survival benefit with manageable toxic effects when compared with non–IFN-α control arms.[24-31] As it became the de facto standard of care worldwide, regulatory agencies have supported the use of IFN-α as the control arm for randomized trials with molecularly targeted therapies that are described elsewhere in this issue.[15-18] The results of these investigations have, in general, established the superiority of VEGF pathway and mTOR targeted agents in previously untreated patients, thereby narrowing the future use of IFN-α as a single agent in this setting.

In recent years, the relative merits of these low- and high-dose cytokine regimens have been clarified by the results of 4 randomized trials (Table 1).[32-35] In the most consequential trial, the French Immunotherapy Group randomized patients with an intermediate likelihood of response to IL-2 and IFN-α to receive medroxyprogesterone (control group), subcutaneous IFN-α, subcutaneous IL-2, or the combination of IFN-α and IL-2.[35] Although significant toxicity was more common in the IL-2 and IFN-α arm, median overall survival did not differ between the arms. The investigators concluded that subcutaneous IFN-α and IL-2 should no longer be recommended in patients with metastatic renal cell carcinoma and intermediate prognosis.

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[32]	CIV IL-2	138	6.5	1	12
	LD SC IFN-?	147	7.5	2	13
	CIV IL-2 + IFN-?	140	18.6	5	17
	MPA	123	2.5	1	14.9
French Immunotherapy Group[35]	LD SC IFN-?	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[33]	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[34]	LD SC IL-2/ IFN-?	91	10	NR	13
	HD IV IL-2	95	23	NR	17.5

Abbreviations: CIV, continuous IV 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.

Taken together, these studies suggest that high-dose intravenous (IV) bolus IL-2 is superior in terms of response rate and possibly response quality to regimens that involve low-dose IL-2 and IFN-α, intermediate- or low-dose IL-2 alone, or low-dose IFN-α alone. Consequently, although low-dose single cytokine therapy has a limited role in patients with metastatic RCC, high-dose IV IL-2 remains a reasonable option for appropriately selected patients with access to such therapy. More significantly, correlative biomarker investigations associated with these trials suggest that the potential exists for identifying predictors of response (or resistance) and thus limiting IL-2 therapy to those most likely to benefit.

Pathologic and molecular predictors of response to IL-2

Influence of Histologic Subtype.

Responses to immunotherapy are most frequently seen in patients with clear cell RCC.[36-38] This observation was detailed in a retrospective analysis of pathology specimens obtained from 231 patients (163 primary and 68 metastatic tumor specimens) who had received IL-2 therapy in Cytokine Working Group (CWG) clinical trials.[38] For patients with primary tumor specimens available for review, the response rate to IL-2 was 21% (30 of 146) for patients with clear cell histologic primary tumors compared with 6% for patients with non–clear cell histologic tumors (1 responder in 17 patients). Among the patients with clear cell carcinoma, response to IL-2 was also associated with the presence of good predictive features (eg, more than 50% alveolar and no granular or papillary features) and the absence of poor predictive features (eg, more than 50% granular or any papillary features). As a result of these data, it may be appropriate for patients whose primary tumor is of non–clear cell histologic type or of clear cell histologic type but with poor predictive features to forgo IL-2–based treatment altogether.

Immunohistochemical markers.

Carbonic anhydrase IX (CAIX) has been identified as an immunohistochemical marker that might predict the outcomes of patients with RCC. In an analysis by Bui et al, CAIX expression in more than 85% of tumor cells (high CAIX expression) has been associated with improved survival and a higher objective response rate in IL-2–treated patients.[39] Building on this work, Atkins et al developed a 2-component model that combined pathology analysis and immunohistochemical staining for CAIX.[40] In a retrospective analysis, this model was able to identifya good risk group that contained 26 (96%) of 27 responders to IL-2 compared with only 18 (46%) of 39 nonresponders (odds ratio, 30; P<.01). A significant survival benefit was also seen for this group (P< .01).

Molecular markers.

Through gene expression profiling of tumor specimens, Pantuck et al were able to identify a set of 73 genes whose expression distinguished complete responders from nonresponders after IL-2 therapy.[41] In their hands, complete responders to IL-2 have a signature gene and protein expression pattern that includes CAIX, PTEN, and CXCR4. A similar analysis identified loss of chromosome 4, 9, and 17p as possible predictors of IL-2 nonresponsiveness.[42] Further investigation into these regions may improve our understanding of the molecular basis of an effective immune response in RCC. Although these approaches require prospective validation, it may become a powerful aid for clinicians in selecting appropriate treatment options for patients with advanced RCC.

Current investigation in patient selection The CWG conducted the high-dose IL-2 "Select" Trial to determine, in a prospective fashion, if the predictive model proposed by Atkins et al 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.[40] The preliminary clinical results of this trial revealed a response rate (28%) that was significantly higher that the historical experience with high-dose IL-2.[43] Analysis of tumor (central pathology review and staining for CAIX) and blood based predictive markers is ongoing to further improve the selection criteria for IL-2 and limit its application to those patients most likely to benefit. As the list of effective therapies for metastatic RCC grows, improvements in patient selection will be necessary to ensure that patients who might attain a durable remission with IL-2 will not miss this opportunity.

IL-2 therapy after VEGF pathway–directed therapy The emergence of molecularly targeted therapies has offered hope for improved clinical outcome for patients with RCC. Vascular endothelial growth factor (VEGF) pathway–directed therapy has been recommended for frontline use in patients with good or intermediate prognosis with other treatments reserved for patients with poor prognostic features or at time of disease progression. However, a retrospective analysis suggests that the toxicity of IL-2 therapy may be higher in patients who have received prior VEGF-targeted therapy, particularly sunitinib, and antitumor activity may be diminished.[44] Although the mechanism for the observed increased incidence of cardiovascular complications remains speculative, the assumption that IL-2 can be given safely after VEGF pathway–targeted therapy may not be valid.

Combination of immunotherapy and targeted/antiangiogenic therapy Although the role of low-dose single-agent cytokines is limited, combinations of cytokines with targeted therapy may have merit. Bevacizumab was combined with high dose IL-2 in a CWG trial. Preliminary results suggest that these two agents can be given safely in combination and produce efficacy improvements that are additive but not synergistic.[45] Two recently completed large phase III trials of interferon plus bevacizumab vs interferon alone have demonstrated superior efficacy with the combination regimen compared with cytokine monotherapy and suggest the potential of an additive effect.[18, 46] Confirmation of the benefit of combination therapy will require a randomized trial comparing the combination to bevacizumab alone.

Investigational immunotherapy

Metastatic RCC has long been a testing ground for novel immunotherapies. Several such approaches, including vaccination and allogeneic bone marrow transplantation, have been tested during the past 2 decades. The initial reports of applying allogeneic bone marrow transplantation were encouraging, but further clinical trials have highlighted the potential toxicity and limited applicability of this approach.[10-12] Vaccination therapy has shown the ability to induce potentially relevant immune responses, although clinical benefit and objective responses have not been consistently observed.[47-49] Avigan et al have conducted a series of clinical trials with a dendritic cell/tumor fusion vaccine approach that have shown encouraging clinical responses in patients with a variety of malignancies, including RCC.[47] To realize the full potential of a vaccine approach in RCC, combinations with immune stimulants (eg, granulocyte-macrophage colony-stimulating factor) and inhibitors of natural T-cell regulation pathways (eg, CTLA4 blockade, T-regulatory cell depletion) may be necessary.

An improved understanding of the molecular mechanisms that govern the interaction between a tumor and host immune response have led to the development of several novel immunotherapies that have recently entered the clinic (Table 2). Obstacles to effective immunotherapy for RCC likely include the physiologic down-modulation of the immune response through the increased expression of molecules such as CTLA4 on the surface of activated T cells. Mechanisms identified as leading to tumor-induced immune suppression have included RCC expression of B7H1 (PDL1), which serves to restrict the cytolytic function of tumor-infiltrating T lymphocytes and stimulation of T-regulatory cell (CD4+ CD25+) production, which limits T-cell receptor signaling.

Table 2. Investigational immunotherapeutic approaches to the treatment of metastatic renal cell cancer

Target	Drug	Class	Development Phase
Blockade of T-cell regulation			
CTLA4[50]	Ipilimumab	Fully human IgG1 mAb	Phase III
PD1[51,52]	MDX-1106	Fully human mAb	Phase I
Inhibition of tumor-induced T-cell function			
TGF-β[53]	GC1008	Fully human mAb	Phase I
TGF-β2	AP12009	Fully human mAb	Phase I
T-cell activation			
CD137[54]	BMS-663513	mAb	Phase II (melanoma)
Cytokines[55]	Interleukin-21	Recombinant molecule	Phase I
Dendritic cell activation			
Toll-like receptor[56]	HYB2055	TLR9 agonist	Phase II

Abbreviations: mAb, monoclonal antibody; TGF, transforming growth factor.

The list of novel agents currently being pursued includes agents that block T-cell regulation (eg, CTLA-4 and PD1 antibodies),[50-52] inhibit tumor-induced immunosuppression (eg, transforming growth factor β antibody, PDL1 antibody),[53] and activate T cells (eg, CD-137 antibody, IL-21)[54,55] and dendritic cells (eg, toll-like receptor agonists).[56] Several of these agents have shown encouraging efficacy signals in early trials. Immune related adverse events associated with CTLA-4 antibodies, including enteritis, skin rash and hypophysitis, have occasionally been life threatening and have also been associated with tumor response.[50] Combination of cytokines and agents that block immune downregulation may prove particularly effective in selected patients. A recent report of high-dose IL-2 and ipilimumab (CTLA4 antibody) in patients with metastatic melanoma revealed manageable toxicity with a complete response rate of 17% suggesting a potential role for this combination in RCC patients.[57] However, the development of targeted immunotherapy for RCC is complicated by the increasing array of other treatment options and their potential impact on the immune system.

Conclusion

RCC has long been considered an immunologically influenced malignancy and thus served as a platform for the clinical testing of anticancer immunotherapy. The nonspecific cytokines, IL-2 and IFN-α, have undergone the most testing and produced only modest benefits for unselected patients. High-dose IL-2 remains the only approach to produce durable responses in patients with metastatic RCC and can thus be considered in appropriately selected patients. For patients unlikely to benefit from, unable to receive, or who progress after IL-2, the emergence of molecularly targeted therapies offers hope for improved clinical outcome.15-18 Additional molecular and pathologic selection opportunities exist for cytokines, but considerable validation work is needed before these selection features can be used clinically. Cytokine therapy optimally should be given in the context of a clinical trial investigating combination therapy and/or patient selection to maximize the benefit of this approach. Targeted immunotherapeutic strategies have been tested in patients with metastatic RCC, but definitive evidence of clinical benefit is only emerging.

In recent years, the list of effective therapies (eg, angiogenesis inhibition; signal transduction inhibition and immunotherapy) for patients with metastatic RCC has increased substantially. The advent of targeted therapy in RCC does not eliminate the potential utility of immunotherapy but rather necessitates efforts to rationally refine this treatment approach through patient selection, combination regimens, and novel agents that together may extend overall survival and increase the cure rate for patients with this disease.

Discussion

Dr. Atkins: The IL-2 Select study represents an important contribution and a well done study. I think we have to assume that there is a reason why some people respond and others don't. You have tissue, blood, DNA, plenty or responders and non-responders and hypotheses to be tested. How do you optimally use these tools to find an answer to why some patients respond and others don't?

Dr McDermott: While we were unable to confirm our primary hypothesis that CA-9 staining predicts for benefit to HD IL-2 we have several other hypotheses that we hope to confirm. If we are successful in this effort, a new model of selection for HD IL-2 will emerge for patients with mRCC.

Dr. Nathanson: Do you have access to a source of material that won't change, which is DNA from the patient? If you think that there might be a phenotype that is predictive of response to immunotherapy that may be inherited you could test for this in your study. You could compare those patients who had excellent responses to those who didn't respond at all and assess whether various inherited factors are affecting outcome. You don't need a big sample–even 50 and 50. I've seen very interesting data come out of small studies with well defined phenotype. Like secondary malignancies, hearing loss after cisplatin; the key is to have a very well defined phenotype.

Dr McDermott: We do have access to DNA for almost all of the patients as we have collected and stored PBMCs on this cohort. If we could obtain the funding for the studies you suggest, we would be glad to collaborate with you on this effort. What you're talking about now, doing genome-wide studies, was not as feasible when this trial was designed but certainly could be pursued in the future.

Dr. Nathanson: As food for thought, if you were giving other immunotherapies IL-2 for renal cancer, do you think the same factors would predict for response?

Dr. McDermott: I would like to think that, but that hypothesis remains to be investigated. Our goal for this study was not to find a predictive marker that was limited to IL-2, but to help identify factors that might help select patients with RCC for immunotherapy. I think this is, ultimately, the way we are going to cure are larger percentage of patients with metastatic disease.

Dr. Stadler: In regard to the endpoint, I wonder whether response is the right metric, or whether it ought to be something else – durable response or 90% response– and I would consider reanalyzing this data using that metric and incorporate some of the other markers you propose to look at.

Dr. McDermott: I agree. Even if the initial result suggests CAIX doesn't predict for response to IL-2, we can still examine the data as you suggest in 2-3 years and report on factors that predict or don't predict for durable response to therapy which is the most important endpoint following HD IL-2 therapy.

Dr. Stadler: OK as long as you're honest that this was not a pre-specified endpoint, its hypothesis generating and it's interesting.

Dr. George: The point is, are people still going to use HD IL-2 off protocol? So, it is still clinically relevant to understand, if nothing else, who is NOT responding and who is, in fact, responding to HD IL-2. Your 6% CR may not be different from a historical number, and your 23 month median PFS may be worse than we've seen. It may just be technique– RECIST vs WHO, but at the end of the day, we do need to understand who we should be selecting, by marker or by clinical parameters, for this treatment.

Dr. Rathmell: I think that we need to bear in mind that a 28% PR rate in a highly selected group of patients, even though it includes a few high risk people, is not as good as sunitinib. A 23 month median survival is about the same as good risk patients achieve with sunitinib. So, we have not achieved a benefit for the majority of patients. What we need to focus on is increasing CRs and very durable PRs.

Dr. McDermott: In my mind there is no comparison between IL-2, good and bad, with any other FDA approved therapy for mRCC. It is more toxic and less likely to produce tumor shrinkage, but it is the only agent that can provide durable benefit. There will be a group, 10-15% of initial cohort that will have durable benefit: people who have responded and have yet to progress. So in the era of targeted therapy, HD IL-2 can still offer a durable benefit and achieve the primary goal of any patient. This is not to say that IL-2 is great. Its weaknesses persist and there are definitely some people who should not get it. However, in the short term, the only mRCC patients who are going to get cured of their disease are the ones who can respond to immunotherapy. Therefore, efforts to understand which patients benefit from this therapy and which do not should be pursued. And therapies that offer durable benefit with less toxicity than HD IL-2 (e.g. PD-1 antibodies) should be aggressively investigated.

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