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Novel Immunotherapeutic Strategies in Development for Renal Cell Carcinoma

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Abstract

Context: The purpose of this report is to review immunotherapies under investigation for patients with renal cell carcinoma (RCC), the most common form of kidney cancer, for which the incidence and mortality rate continue to increase.
Objective: To summarize and evaluate current data on immunotherapies for RCC and discuss issues to be resolved before integration into the RCC treatment paradigm.
Evidence acquisition: A search of Medline, clinicaltrials.gov, and congress abstracts/treatment guidelines was performed in May 2012 using the following terms (and variations): metastatic renal cell carcinoma, practice guidelines, response/resistance to current treatments, immunotherapy, novel immunotherapeutic strategies, T-cell modulation, immune priming, innate immunity, and combination therapy.
Evidence synthesis: Prior to the advent of novel agents targeting the vascular endothelial growth factor and mechanistic target of rapamycin pathways, interleukin-2 (IL-2) and interferon-α were the mainstays of RCC treatment. IL-2 remains one of the only treatments capable of curing advanced RCC, albeit in few patients. Despite recent advances, unmet need still exists for patients in the adjuvant setting, those with poor prognostic factors, and those who have progressed on prior targeted therapies. Improved understanding of host–tumor immune interactions has led to development of novel immunotherapeutic agents, including antibodies against immune checkpoint proteins (eg, programmed death-1 and cytotoxic T-lymphocyte antigen-4), and various vaccines. Because many of these compounds are in development, clinical experience with them is limited, although some have demonstrated activity in preliminary studies.
Conclusions: It is not yet clear where these new immunotherapies will fit into RCC treatment paradigms, but they may provide new options for patients whose current choices are limited. Furthermore, predictive biomarkers are needed to identify patients who will derive the greatest benefit from immunotherapy.
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1. Introduction

Renal cell carcinoma (RCC) is the most common form of kidney cancer, accounting for approximately 3% of adult malignancies [1]. Within RCC, clear cell histology is most prevalent, accounting for 80–90% of cases [2,3]. Despite the lack of RCC screening, most patients present with localized RCC and many can be cured with radical nephrectomy [4]. However, 20–30% of patients treated with surgery will relapse, despite having no evidence of metastases at diagnosis [5]. Long-term outcomes for patients who develop metastatic RCC (mRCC) are variable. Historically, approximately 25–30% of patients will have mRCC at diagnosis [1], with an estimated 5-yr survival rate of 10% [6]. Because most clinical trials for targeted therapies and immunotherapies have been conducted in patients with

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clear cell RCC (ccRCC), this article will focus mainly on this subtype.

Prior to the development of targeted therapies, interleukin-2 (IL-2) and interferon-α (IFN-α) were the principal standards of care for advanced RCC. Treatment with high-dose (HD) IL-2 has demonstrated antitumor activity in some patients, with a durable response in a small percentage of them [7–9]. A small subset of patients achieve complete remission (3-yr durable complete responses [CRs] in approximately 7%) with HD IL-2 therapy [7,8]. Because IL-2 must be administered at specialized centers and has substantial toxicity, treatment is often reserved for those patients who are most likely to benefit and can manage the higher toxicity profile (ie, cc histology, good performance status, and normal organ function) [3,5]. HD IL-2 is currently the only therapy for mRCC that can achieve a predictable cure rate [7,8], indicating that immunotherapy could have a critical role in RCC treatment.

IFN-α and IL-2 currently are the only immunotherapies discussed in current RCC treatment guidelines: IFN-α in combination with the antivascular endothelial growth factor (VEGF)-A monoclonal antibody (mAb) bevacizumab is recommended as a first-line treatment for patients with favorable- to intermediate-risk metastatic ccRCC [2,3,5,10], whereas HD IL-2 [2,5,10] or IFN-α monotherapy [3] can be used for selected patients with good performance status and favorable-risk metastatic ccRCC. Somewhat weaker evidence supports the use of IFN-α or IL-2 monotherapy in selected patients who have progressed on first-line therapies (National Comprehensive Cancer Network [NCCN] category 2B) [5]. For comparison, immunotherapy is not currently considered for patients with non-ccRCC [5,10] outside of the European Organization for Research and Treatment of Cancer Genito-Urinary Group guidelines, which suggest first-line bevacizumab plus IFN-α (as an alternative to sunitinib) or HD IL-2 for use in selected patients with good performance status [2].

Improved understanding of RCC pathogenesis has resulted in the development of novel targeted agents for use in advanced disease. Agents targeting angiogenesis and signal transduction pathways have markedly improved patient outcomes, particularly progression-free survival (PFS), relative to IFN-α or placebo [11]. Nevertheless, CRs to targeted therapies are rare, and most patients develop progressive disease shortly after an initial response [11,12]. Recent insight into tumor–host interactions has prompted novel immunotherapeutic strategies for cancer, several of which are potentially applicable to RCC. Treatment with ipilimumab, a fully human, anticytotoxic, T-lymphocyte antigen-4 (CTLA-4) mAb, has improved overall survival (OS) in metastatic melanoma (mMEL) and there is evidence of cancer regression in patients with RCC [13,14]. The aim of this article is to provide a comprehensive overview of novel immunotherapies for RCC.

2. Evidence acquisition

A systematic literature review was performed in May 2012 using the Medline database, clinicaltrials.gov, and abstract searches of the major cancer conferences organized by the American Society of Clinical Oncology and the European Society of Medical Oncology, and the most recent guidelines of relevant medical specialty organizations. The Medline search strategy included the following terms: metastatic renal cell carcinoma, practice guidelines, response/resistance to current treatments, immunotherapy, novel immunotherapeutic strategies, T-cell modulation, immune priming, innate immunity, and combination therapy. The search results were restricted to the English language, with preference given to articles published within the last 5 yr.

3. Evidence synthesis

3.1. Unmet needs in renal cell carcinoma

Molecular therapies that block the VEGF or mechanistic target of rapamycin (mTOR) pathways are currently considered mainstays of advanced RCC treatment [2,3,5,10]. For patients with metastatic ccRCC at favorable or intermediate risk (according to the Memorial Sloan-Kettering Cancer Center [MSKCC] model) [5,15], current first-line therapy guidelines recommend monotherapy with the tyrosine kinase inhibitors (TKIs) sunitinib or pazopanib, or combination treatment with IFN-α and bevacizumab [2,3,5,10]. These recommendations are based on phase 3 trial data showing a significantly longer PFS with sunitinib versus IFN-α (11 vs 5 mo) [2,16,17], and with pazopanib versus placebo in treatment-naïve patients (11.1 vs 2.8 mo) [5,18]. Similarly, in another phase 3 trial, bevacizumab plus IFN-α significantly increased median PFS compared with IFN-α alone (10.2 vs 5.4 mo, respectively; $p < 0.0001$), but did not show benefit in high-risk patients [3]. Patients with poor prognostic factors make up approximately 20% of mRCC cases and more effective treatment options are needed for them. Currently, the mTOR inhibitor temsirolimus is the only NCCN category 1, first-line therapy recommended for poor-risk patients [2,3,5,10].

Durable responses to targeted therapies are rare and most patients eventually develop progressive disease [11]. Three patterns of resistance to VEGF- and VEGF receptor (VEGFR)-targeted therapies have been described, including (1) initial resistance to therapy, (2) early response followed by progression 6–12 mo later, and (3) stable disease (SD) over months to years followed by eventual progression [19]. A clear need exists for effective agents for patients who have progressed on multiple lines of targeted therapy. Everolimus is recommended as second-line therapy for patients who progress on first-line treatment with a TKI or VEGF inhibitor [2,3,5,10], whereas sorafenib and pazopanib are recommended in patients who progress after cytokine therapy [2,3,5,10]. Sunitinib is an alternative in some guidelines [5,10]. No recommendation exists for patients progressing on mTOR inhibitors.

It is clear at this juncture that more effective options are needed for patients who do not fit in the favorable- or intermediate-risk categories, while therapies that extend survival for longer periods beyond the current standard treatments can also be improved.

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