Renal cell carcinoma: immunotherapy revisited

> "*Development of a new treatment paradigm has stimulated the interest of investigators and clinicians in renal cell carcinoma...*"

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The overall incidence of renal cancer appears to be slowly increasing, and neoplasms of the kidney currently account for 3% of all malignant tumors. The estimated incidence in the USA in 2009 was 57,760 new cases, with 12,890 deaths reported [1]. Historically, patients with renal cancer presented with the classic triad of symptoms including flank pain, hematuria and a palpable abdominal mass, but recently, increasing numbers of individuals are being diagnosed when asymptomatic with an incidentally discovered renal mass. Advances in imaging and techniques have increased the percentage of patients who are eligible for surgical intervention, but a significant percentage of patients still present with surgically unresectable disease [2], and the development of metastatic disease remains a major problem.

In addition to a variety of clinical prognostic factors, the importance of histology in predicting the biologic characteristics and clinical behavior of renal cancer was recognized in the last decade. Renal cell carcinoma (RCC) includes a variety of histologic subtypes, each having unique morphologic and genetic characteristics [3]. Clear cell renal carcinoma, the most common variant, arises from the proximal convoluted tubule, and accounts for 70–85% of renal epithelial malignancies. Papillary renal cancer is the second most common type, comprising 10–15% of renal tumors. The association of histologic subtype and gene alterations (e.g., *VHL* gene mutations) provided the basis for the development of a new treatment paradigm for metastatic RCC (mRCC) involving targeted therapy [4]. The clear cell histologic variant with its high frequency of *VHL* gene mutation or inactivation is susceptible to such approaches.

Since the 1980s, immunotherapy with cytokines such as IFN-α or IL-2 was the primary treatment for mRCC [5,6]. Currently, agents that target the VEGF pathway are the principal therapeutic modalities utilized [7]. Since December 2005 regulatory approval of five new agents and one new regimen by the US FDA and/or EMA has occurred. The TKI sunitinib is the current standard of care for untreated mRCC patients [8]. Despite its impressive clinical activity, few durable and long-term complete responses have been identified. An impact on overall survival has been identified when compared with IFN-α. Two additional TKIs (sorafenib and pazopanib) have also received regulatory approval as treatment for mRCC; however, they are most frequently utilized in refractory patients [9,10]. Inhibition of the VEGF pathway by ligand-binding antibodies such as bevacizumab has also been extensively explored and in combination with IFN-α is an additional regimen for the management of this epithelial malignancy [11].

Alternative pathways capable of leading to tumor growth and proliferation in RCC have also been identified. The mTOR kinase, which may be constitutively activated in RCC by deregulated activation of the PH-domain serine/threonine oncogenes, Akt and PDK-1, or loss of the tumor suppressors PTEN and TSC1/TSC2, plays a role in the regulation of protein translation [12]. Two rapamycin analogs, temsirolimus and everolimus, have been approved by both the FDA and EMA as therapeutic options for selected subsets of mRCC patients (e.g., poor risk and TKI refractory) [13,14].

The current treatment paradigm for mRCC provides control of tumor progression, improves progression-free survival, and has an impact on overall survival. Few patients develop complete lasting regressions or cure, and therefore methods to improve outcomes are needed. The use of combinations and identification of optimal treatment sequences are under study. Importantly, novel agents targeting other pathways responsible for tumor progression as well as extracellular matrix proteins involved in angiogenesis, proliferation and metastasis are also under investigation. In addition, the role

of immune therapy and immunoregulation in mRCC is again under study. In this setting, the three articles by Pickering [15], Schwaab [16] and Battelli [17] provide further insights on the evolving field of mRCC therapeutics, and the renewed interest in immunotherapy.

Pickering and colleagues have provided an excellent perspective on the evolution of mRCC therapy over the next 5–10 years [15]. They review the developments during the last decade, and point out the advantages as well as the shortcomings of currently available therapy. They note a marked increase in available targeted therapies against the VEGF or mTOR pathways, which have anti-tumor activity and importantly, have a meaningful impact on overall survival. Significantly, they correctly point out that high dose IL-2, remains the only treatment modality able to induce durable complete remissions and cure mRCC in a small number of patients [5]. They also highlight the current investigations attempting to improve the efficacy of current therapy. These include the development of validated biomarkers, and investigation of novel immunomodulatory agents that may potentially enhance current treatment strategies. The potential role of VEGF receptor-targeted therapies such as sunitinib in stimulating host immune response may justify their combination with cytokines or newer immunomodulating strategies and vaccines. The immune checkpoint inhibitors, including the CTLA-4 and PD-1 monoclonal antibodies, have also demonstrated activity in early clinical trials in patients with mRCC.

In this same context, Schwabb and Ersntoff review the evolution of therapeutic vaccines in RCC [16]. The recent regulatory approval of Provenge® (Sipuleucel-T) for patients with metastatic prostate cancer [18] has stimulated interest in the development of tumor vaccines, especially in malignancies such as RCC. This article summarizes the current understanding of immune recognition and regulation, and how it relates to vaccine development in patients with mRCC. The goals of an anticancer vaccine are outlined within the biologic context of the immune response. Importantly, the issue of immune suppression in mRCC, including the roles of immunoregulatory cells as well as the tumor microenvironment, is discussed. In order to speculate on future vaccine strategies, the authors also provide a review of recent efforts in this field including use of autologous RCC cells [19], and the 5T4 oncofetal antigen (TroVax®) [20]. The design of these

two clinical trials was quite different, with the former including RCC patients at risk of relapse after surgery [19], and the latter patients with mRCC [20]. The study investigating MVA-5T4 randomized 733 patients to either placebo plus systemic therapy, or the MVA-5T4 vaccine in combination with systemic therapy. Systemic treatment consisted of either sunitinib, IFN-α or IL-2 and the primary end point was overall survival. The overall results did not demonstrate superiority for the vaccine combination, but a *post hoc* analysis suggested an antibody response to the MVA-5T4 vaccine was associated with improved survival. One additional vaccine trial [21] not discussed by these authors, was the Phase III open label trial utilizing vitespen (autologous, tumor-derived heat shock protein gp96-peptide complexes) in patients at high risk of recurrence after resection of locally advanced RCC. The trial compared the vaccine derived from autologous tumor with no adjuvant treatment (observation) in 728 patients. The primary end point was disease-free survival. The study was negative, but subset analysis did identify a group of patients with potential benefit. These previous RCC vaccine trials demonstrate that investigators should not only evaluate the role of vaccine components (i.e., antigen, antigen delivery vehicle and immune costimulants) on the immune response, but also consider the issues of study design and the trial end points. The authors point out that the next generation of vaccines must balance induction of anti-tumor immunity, autoimmunity and generation of immune tolerance [16]. They speculate that dendritic cell-based vaccines hold the most promise for production of cancer-specific and clinically relevant immune stimulation. Finally, they note that vaccine approaches for RCC are now undergoing a well-deserved renaissance, in the setting of an improved understanding of tumor immunology. This point is clearly illustrated by two recent Phase III vaccine trials proposed for patients with mRCC, both of which investigate a vaccine administered with sunitinib. The role of the TKI in this setting is not only as an anti-tumor agent, but also an agent that has reproducible immunoregulatory effects on various cell populations [22]. The first trial will investigate the combination of the approved TKI, sunitinib, with an autologous RNA electroporated dendritic cell based immunotherapy, AGS-003 [23]. The primary objective in this study is to estimate the median progression-free survival with this combination compared with sunitinib alone in patients with newly diagnosed advanced RCC

and synchronous mRCC. A second trial will examine the effects of a multipeptide vaccine (IMA-901) plus GM-CSF in combination with sunitinib compared with sunitinib alone [101] in HLA-A2 positive mRCC patients. The primary end point of this trial is overall survival. The current generation of vaccine trials are focused on mRCC rather than patients following neph-rectomy and at high risk of relapse. If the ongoing post-operative adjuvant studies with sunitinib, sorafenib or pazopanib in RCC demonstrate efficacy, then vaccine TKI combinations in this setting will likely be pursued.

Finally, Battelli and Cho review the role of mTOR inhibitors in RCC [17]. This is relevant given the increasing role the rapalog compounds are playing in the treatment of mRCC. In their review, the role of the PI3-K/Akt/mTOR path-way is highlighted, and the clinical results with everolimus and temsirolimus in advanced RCC reviewed. Finally the authors speculate on the future directions in terms of sequen-tial therapy, combinations and development of novel therapeutic agents. One interesting fact highlighted, is the effect of rapamycin on the immune response. It was initially developed as an immunosuppressive drug used to prevent graft rejection in solid organ transplant recipi-ents. However, in the last few years, a complex immunomodulatory role of mTOR inhibitors has been described. As an example, the authors cite a study by Araki *et al.* [24], demonstrating that mTOR is a major regulator of memory CD8 T cells and that the rapalogs appear to have immunostimulatory effects on the generation of memory CD8 T cells. The possibility that this class of agents may also have immunoregulatory activity exists, and provides a rationale for fur-ther investigations in combination with various immunotherapeutic approaches.

In summary, the three reviews discussed focus on the exciting developments in the field of mRCC therapeutics. Development of a new treatment paradigm has stimulated the interest of investigators and clinicians in RCC, and has been accompanied by a resurgence of interest in the role of immunotherapy for patients with both advanced and localized RCC based on the current understanding of immunoregulation.

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