Renal cell carcinoma (RCC) constitutes 80 to 85 percent of primary renal neoplasms in adults (1). Although surgical resection can be curative in localized disease, many patients eventually recur. Patients with locally advanced or metastatic disease have a poor prognosis, with a 5-year survival rate of less than 15%. Because RCC is highly resistant to both chemotherapy and radiation therapy (2), immunotherapy might have the highest potential as a novel treatment for RCC (3). Accumulating evidence indeed shows that effector cells of the immune system play an important role in the recognition and elimination of neoplastic cells. Particularly in RCC, experimental data suggest that the immune system might be extremely important in controlling the disease in situ (4). For example, in RCC, major T cell infiltrates can be demonstrated in the tumor. The presence of antigen-specific T cell clones has been shown in both primary lesions and draining lymph nodes, and these clones are able to lyse renal carcinoma cells in vitro (5,6). Unfortunately, in the long term, the immune response against RCC fails to limit disease progression.

To date, several immunotherapeutic approaches have been proposed to treat RCC (3,7), particularly since different RCC-related tumor antigens have been identified that can be targeted, processed and presented by immune effector cells (8). It is well known that of these immune effector cells, dendritic cells (DCs) play an orchestrating role in regulating T cell responses, partly due to their potent antigen-presenting capacity (9). The attractive concept of autologous monocyte-derived DC-based tumor vaccination resulted in an increasing number of phase I/II trials with different approaches regarding the vaccine composition, including the nature of the antigen(s) (7). Synthetic peptides are commonly used to load DCs in DC-based vaccination trials, but are mostly HLA-A*0201-restricted which limits their clinical use. The use of tumor lysate circumvents this restriction and has the advantage of inducing a polyclonal immune response. Similarly, the use of total renal tumor RNA-transfected DCs has proven to induce T cell activities directed against a broad set of renal tumor-associated antigens (10). In the AGS-003 strategy, autologous DCs co-electroporated with the patients’ amplified tumor mRNA and synthetic CD40L RNA are employed (11). Although encouraging results are reported upon administration of this vaccine with regard to immune response as well as survival (12), results from the phase III trial have not been published yet (http://clinicaltrials.gov/ct2/show/NCT01582672).

Recently, the first autologous DC-based therapy was approved by the Food and Drug Administration (FDA) for treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T (known by the trade name, “Provenge”) is a cellular vaccine which is created upon collection of patient’s white blood cells and subsequent in vitro incubation of these cells with a fusion protein that combines prostate acid phosphatase (PAP) with recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF). Upon re-infusion of this cell product into the patient, sipuleucel-T stimulates the patient’s own immune system to specifically recognize and combat his cancer. As was published in the New England Journal of Medicine, sipuleucel-T prolonged median survival by 4.1 months
CD4+ T cell help can be achieved by using synthetic long peptides (SLPs) (21). Following in vivo uptake by DCs, a proportion of the SLPs is processed and loaded into MHC class II molecules, allowing fragment presentation to CD4+ T helper cells. Another part of the ingested SLPs is digested by the proteasome in the cytosol and the endoplasmic reticulum. This is followed by loading of 8-10 amino acid-long peptides into MHC class I molecules, which allows fragment presentation to CD8+ cytotoxic T cells (22).

Nevertheless, the increase in median overall survival in the patients treated with IMA901 was not associated with standard measures of efficacy, including changes in size and volume of measurable lesions. This uncoupling effect on survival and disease progression appears to be a common property of immunotherapy, and is designated as a delayed treatment effect. Indeed, biological effects of cancer vaccines are not related to their pharmacokinetics, and effectiveness may take weeks or months to become apparent (23). Hence, effectiveness as measured by tumor regression at traditionally early time points may fail to demonstrate any measurable potentially beneficial effect. For this, studies are intensified to develop new, non-invasive diagnostic tests, e.g., biomarkers, to carefully monitor the effect of the vaccination strategy on the tumor. The feasibility and value of a comprehensive biomarker program has been underscored by Walter et al., as indicated by the identification of two biomarkers, APOA1 and CCL17, that are potentially predictive for vaccine-induced immunity and overall survival.

Furthermore, studies that improve or refine immunotherapeutic outcomes in the clinic are warranted. Simple methods that are likely to increase efficacy include (I) administration of boost vaccinations in order to extend the response; (II) treating patients earlier in their disease course; (III) and combination strategies with agents that are known to activate, accelerate, and augment immune responses (24). These include adjuvants (IL-7, IL-12, IL-15, and monophosphoryl lipid) to augment T cell responses, and antagonists of negative regulators of T cell activation [anti-CTL-associated receptor 4 (CTLA-4) and anti-programmed death 1 (PD1) receptors], as well as agents to neutralize immunosuppressive cytokines (anti-IL-10 and anti-TGF-β) that are important in winding down immune responses. Walter and colleagues (14) improved the efficacy of the IMA901 vaccination by means of a single-dose cyclophosphamide. Indeed, the median overall survival of the patients treated with IMA901 and cyclophosphamide was 23.5 months compared to 14.8 months in the patients treated with IMA901 and cyclophosphamide. Indeed, the median overall survival of the patients treated with IMA901 and cyclophosphamide was 23.5 months compared to 14.8 months in the patients.
treated without cyclophosphamide. It has been postulated that this immunomodulator counteracts the regulatory mechanisms that oppose successful immunotherapy, e.g., by reducing the numbers of regulatory T cells (Tregs) (25).

In conclusion, it remains to be established from ongoing phase III trials whether the DC-based vaccine AGS-003 or the peptide vaccine IMA901 results in the best treatment for advanced renal cell carcinoma with the highest overall survival benefit. However, it is likely that vaccination approaches will become part of the armamentarium of nephrologists, urologists and medical oncologists who manage and care for renal cancer patients.

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None.

Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

References


