Editorial

Does patient-tailored immunotherapy pave the way for new renal cell carcinoma treatment perspectives?

Ilse Van Brussel[1], Amaryllis H. Van Craenenbroeck[2], Dorien M. Schrijvers[3], Nathalie Cools[4]

[1]Laboratory of Pharmacology, University of Antwerp, B-2610 Antwerp, Belgium; [2]Division of Nephrology-Hypertension, Antwerp University Hospital, B-2650 Edegem, Antwerp, Belgium; [3]Laboratory of Physiopharmacology, University of Antwerp, B-2610 Antwerp, Belgium; [4]Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, B-2610 Antwerp, Belgium

Correspondence to: Ilse Van Brussel. Laboratory of Pharmacology, Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium. Email: ilse.vanbrussel@ua.ac.be.

Submitted Sep 10, 2012. Accepted for publication Oct 11, 2012.
doi: 10.3978/j.issn.2223-4683.2012.10.02
Scan to your mobile device or view this article at: http://www.amepc.org/tau/article/view/1138/3140

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 compared with results in placebo-treated patients (13). In summary, the advantage of DC-based immunotherapeutic strategies is good tolerability and observed survival benefit. Unfortunately, these patient-tailored therapeutics are very time-consuming and costly. As an alternative, targeting DCs *in vivo* may be more attractive from a cost-effectiveness perspective, since this approach would omit tailor-made *ex vivo* culturing. Indeed, such off-the-shelf therapeutic vaccines have shown preliminary evidence of efficacy (13), providing hope that improvements in patient outcomes with this modality may lead to therapeutic options that are less resource-intense. Walter *et al.* (14) developed IMA901, a peptide vaccine for RCC, consisting of nine HLA-A*02-restricted tumor-associated peptides (TUMAPs) and one HLA-DR-restricted TUMAP in combination with administration of GM-CSF. GM-CSF is used to stimulate antigen-presenting cells (APCs), including DCs (15), *in vivo*. Subsequently, TUMAPs bind to major histocompatibility complex (MHC) molecules on the cell surface of APCs, and in turn the activated APCs facilitate *in vivo* priming of T cells. Hence, the designated purpose of IMA901 is to elicit a therapeutic immune response to antigens expressed by cancer cells. The authors report stabilization of the disease or a partial response to therapy in 43% of the 28 patients that received eight intradermal IMA901 vaccinations. In the remainder 57% of subjects, RCC progressed (14). Furthermore, subjects that responded to multiple TUMAPs were significantly more likely to experience disease control than subjects that responded to only one TUMAP or showed no response (14), indicating that the enhancement of the breadth of immune responses targeted to antigens introduced by the vaccine is of great consequence.

Strong and broad T cell responses will prevent immune escape by certain cancer cells that have altered their cell surface expression of certain HLA molecule(s). Although Walter *et al.* have not addressed the added value of inclusion of the HLA-DR-restricted TUMAP, others have demonstrated the importance of $CD4^+$ T cell help in the stimulation of such strong and effective cellular immune responses. $CD4^+$ T helper cells deliver help for $CD8^+$ cytotoxic T cells by fully activating DCs through the CD40-CD40 ligand signaling pathway as well as by the secretion of interleukin-2 (16). Pan HLA-DR epitope (PADRE) peptides, that are capable of binding to different MHC class II molecules with high-affinity (17), have been used in conjunction with other forms of vaccines to enhance vaccine potency in preclinical models (18,19) and they have also been used in clinical trials with minimal toxicity (20). Alternatively, $CD4^+$ 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 endoplasmatic 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 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.

Acknowledgements

None.

Footnote

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

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Cite this article as: Van Brussel I, Van Craenenbroeck AH, Schrijvers DM, Cools N. Does patient-tailored immunotherapy pave the way for new renal cell carcinoma treatment perspectives? Transl Androl Urol 2013;2(2):85-88. doi: 10.3978/j.issn.2223-4683.2012.10.02