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Review – Kidney Cancer

Therapeutic Dendritic Cell Vaccination of Patients with Renal Cell Carcinoma

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Abstract

Objective: Dendritic cell (DC) vaccination against cancer is a new specific immunotherapeutic approach given with either therapeutic or adjuvant intent. We provide a review of DC vaccination as a treatment for metastatic renal cell carcinoma (RCC).
Method: A total of 197 patients with metastatic RCC were treated with DC vaccination in 14 phase I/II clinical trials. Different vaccine preparations, administration routes, and treatment schedules have been tested in these trials. Clinical response and immune response were analysed.
Results: Seventy-three (37%) patients had clinical response with 4 complete responses, 8 partial responses and 61 disease stabilisations, whereas 4 patients had mixed response, but most of these responses have not been transformed into durable clinical effects. Immune responses were observed in a subset of the treated patients but were not always associated with a clinical response. Only mild toxicity was observed in these trials.
Conclusion: DC vaccination therapy in patients with metastatic RCC is currently experimental but the results are encouraging with achievement of tumour regression and induction of antigen-specific immune response combined with minimal toxicity in a subset of the treated patients. Future emphasis should be placed on therapy in the adjuvant setting because patients with minimal residual disease are more likely to benefit from the treatment. Combination approaches with DC vaccination and immune-enhancing therapies or antiangiogenic therapy should be further investigated to develop new and more efficient treatment strategies for patients with RCC.

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1. Introduction

Renal cell carcinoma (RCC) is a relatively rare disease, comprising approximately 2% of all malignancies. Histologically, clear cell RCC represents 75–85% of the tumours and is frequently associated with inactivation of the von Hippel Lindau (VHL) tumour suppressor gene, leading to overexpression of vascular endothelial growth factor (VEGF) [1]. There is a great variability in the clinical behaviour of RCC but risk of tumour recurrence is closely related to state of the disease. Localised disease is treated by surgery and the standard management after nephrectomy is surveillance. More than 30% of the patients present with metastatic disease at diagnosis and up to 50% of diagnosed patients develop metastatic disease with a poor prognosis and a median survival time of only 9 mo. The disease is highly resistant to chemotherapy with response rates <10%, a short duration of response, and no effect on overall survival [2]. Immunotherapy using interferon α (IFN-α) and interleukin 2 (IL-2) is considered the standard therapy for metastatic RCC, but for patients who progress after an initial response or who fail to respond, no effective treatment is available. New therapies targeting VEGF in RCC are now entering clinical phase II/III trials. VEGF is a key regulator of both normal and tumour-associated angiogenesis and exerts its effect through receptors present on the cell surface. These transmembrane tyrosine kinase receptors include VEGFR-1 (flt-1) and VEGFR-2 (KDR/flk-1). VEGF can be inhibited by binding of the VEGF protein, blocking the receptor, or inhibiting VEGFR signalling through their tyrosine kinases. These strategies have been tested clinically in metastatic RCC and there is evidence of antitumour effect and a prolonged progression-free survival although data are too preliminary to evaluate the effect on overall survival [3].

2. Immunologic treatment

Spontaneous remissions of advanced RCC [4] and infiltration of cancer tissue with lymphocytes and dendritic cells (DCs) have been described [5]; therefore, immune mechanisms have been suggested to play a role in the natural disease course of RCC. Both IFN-α and IL-2 show clinical activity in metastatic RCC and are currently the standard therapy. The mode of action of IFN-α is poorly understood, but it is probably a combination of stimulation of cell-mediated cytotoxicity, direct antiproliferative antitumour activity, and an antiangiogenic effect. A meta-analysis showed that the response rate for regimens containing IFN-α was 14% [6]. IL-2 is a cytokine with high biologic activity and is the principal stimulator of T-cell growth; it has profound effects on T-cell, B-cell, and macrophage activation. Most studies have reported overall response rates of 10–22% with durable responses in a small subset of patients [7]. High-dose IL-2 bolus treatment is associated with a high incidence of toxic side effects such as hypotension, lung oedema, vascular leak syndrome, and renal and hepatic side effects, whereas low-dose IL-2 treatment is better tolerated [8]. Patients with clear cell tumours are known to have a significantly better prognosis than other histologies and respond better to treatment based on IL-2 [9], but reliable predictive markers of a patient's probability to respond to immunotherapy are currently unavailable. Because only a minority of patients treated with immunotherapy have a favourable response and few achieve long-term survival, new therapeutic approaches are urgently needed.

3. Tumour antigens

Human tumours express a variety of tumour antigens recognisable by the immune system, and these antigens are potential targets for cancer vaccination therapy. Several characteristics make a tumour antigen particularly attractive as a vaccine target: lack of pre-existing tolerance, differential expression on tumour versus normal tissue, and a role in tumourigenesis [10]. A number of tumour antigens, such as carbonic anhydrase IX (CAIX), telomerase, and survivin [11–13], are overexpressed in RCC and are potential targets for peptide-based vaccination. Another approach is to use undefined tumour antigens from autologous or allogeneic tumour lysate, whole apoptotic or necrotic tumour cells, or DC-tumour fusion products as antigens. This method aims to deliver a broad spectrum of tumour-derived epitopes to generate a broader T-cell immune response [14].

4. Tumour escape

Spontaneous immune responses against tumour antigens are frequently induced in cancer patients. Despite the presence of tumour-specific antigens, the immune response may, however, not correlate with a clinical antitumour response. This is due to several mechanisms by which tumours can escape immune surveillance and destruction. Antigen-presenting