Dendritic cell vaccination of patients with renal cell carcinoma

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ABSTRACT

A large number of dendritic cell (DC) based vaccines have been tested in cancer patients in clinical phase I/II studies and a few randomised phase III studies. Results from these studies indicate that it is possible to induce antigen-specific immune response and tumour regression in a subset of the treated patients. Recent evidence has demonstrated that regulatory T-cell (Treg) mediated immunosuppression may be one of the crucial tumour immune evasion mechanisms and one of the obstacles of successful immunotherapy in cancer patients.

In the first part of this PhD study, a clinical phase I/II study with a DC based vaccine combined with IL-2 treatment for patients with mRCC was established. The second part of this thesis was focused on selected immunosuppressive mechanisms in metastatic renal cell carcinoma (mRCC) patients following DC vaccination and low-dose IL-2 treatment. The impact of this treatment on Treg cells in peripheral blood in mRCC patients was assessed. T-cell receptor (TCR) clonotype mapping was performed to evaluate the dynamics of Treg cell clonotypes in peripheral blood.

Thirty patients with progressive mRCC were included in the phase I/II trial and twenty-seven of these patients were evaluable. The patients were treated with DCs pulsed with peptides or tumour lysate combined with low-dose IL-2. The treatment was feasible, safe and without severe toxicity. Almost half of the patients obtained stable disease during therapy, which persisted in one third of the patients. Antigen specific immune responses were observed in a subset of the treated patients. Significant response associated changes in serum IL-6 and YKL-40 were observed during treatment and serum IL-6 and YKL-40 may be potential response biomarkers during DC vaccination therapy. The immune response observed in some of these patients, the decline in serum IL-6 in patients obtaining SD, and the fact that all patients had progressive disease when entering the protocol makes it likely that stable disease was induced by the vaccination therapy. However, the phase I/II study design does not allow firm conclusion on clinical benefit; therefore, additional studies are needed to further evaluate this question.

Administration of DC vaccination combined with low-dose IL-2 to patients with mRCC mediates a significant increase of Treg cells in peripheral blood in vivo. Clonotype mapping of Treg cells revealed a remarkable heterogeneity over time and no persistent Treg cell clonotypes appeared, indicating that there is a rapid turn-over of these cells. Treg cells may hinder generation of anti-tumour immune responses and in part explain why tumour regression after therapeutic DC vaccination is rare. Therefore, approaches combining DC-mediated immunotherapy and depletion of Treg cells may enhance the ability to elicit anti-tumour responses in cancer patients.