ABSTRACT OF DISSERTATION

Studies of a T-lymphocyte cell-line in the treatment of patients with metastatic melanoma: clinical and immunologic response

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ABSTRACT

The PhD dissertation is based upon investigations carried out during my employment as a research fellow at the Department of Oncology, Aarhus University Hospital, Aarhus, Denmark. Investigations aimed at examining clinical and immunological features of a new treatment principle in stage IV melanoma. Clinical examinations consisted of a phase I dose escalating trial designed to assess efficacy, feasibility and toxicity of intra-tumoral injections of allogeneic, cytotoxic T lymphocytes capable of recognizing melanoma cells expressing the tumor associated antigen MART-1 at their surface. A capability conveyed through the transduction of a T cell receptor-encoding gene. Fifteen patients with stage IV melanoma were included in the clinical trial and the treatment principle was found feasible, safe and capable of inducing tumor regression. One patient obtained a partial response encompassing both metastases used and not used for injections. In addition, regression of metastases used for injections in two patients and regression of a metastasis not used for intra-tumoral injections in one patient, was observed. Immunological investigations were carried out using blood and tumor tissue sampled before and during treatment and aimed primarily at elucidating the extent to which local intra-tumoral injections were capable of causing local and/or systemic immunologic reactions. Immunohistochemical analyses of formalin fixed and paraffin embedded tissue samples revealed how the number of infiltrating CD8+ T lymphocytes and Natural Killer cells (CD57+) increased significantly from day 1 to 14 in metastases used for intra-tumoral injections, while the number of immune cells in metastases not used for injections did not change significantly during treatment. Additional analyses were carried out in cooperation with the Tumor Immunology Group at the Institute of Biological Cancer Research, formerly at The Danish Cancer Society. ELISPOT analyses displayed increases in the amount of functional MART-1 specific T lymphocytes, while in contrast, fluorescence activated cell sorting (FACS) could not demonstrate the emergence of MART-1 specific T lymphocytes. TCR clonotype mapping showed a dynamic picture but was not conclusive regarding a treatment induced systemic response. The overall conclusions of the dissertation is that injection of allogeneic, cytotoxic, MART-1 specific T lymphocytes was feasible, safe and capable of inducing tumor regression. It appeared that the treatment did induce a local - and to some extent also a systemic - clinical as well as immunological response in some of the treated patients. Further investigations in a phase II setting, combined with known immune activating substances as Interleukin-2, are warranted.