Heat Shock Protein 70 (Hsp70) Peptide Activated Natural Killer (NK) Cells for the Treatment of Patients with Non-Small Cell Lung Cancer (NSCLC) after Radiochemotherapy (RCTx) - From Preclinical Studies to a Clinical Phase II Trial.

Abstract:
Heat shock protein 70 (Hsp70) is frequently overexpressed in tumor cells. An unusual cell surface localization could be demonstrated on a large variety of solid tumors including lung, colorectal, breast, squamous cell carcinomas of the head and neck, prostate and pancreatic carcinomas, glioblastomas, sarcomas and hematological malignancies, but not on corresponding normal tissues. A membrane (m)Hsp70-positive phenotype can be determined either directly on single cell suspensions of tumor biopsies by flow cytometry using cmHsp70.1 monoclonal antibody or indirectly in the serum of patients using a novel lipHsp70 ELISA. A mHsp70-positive tumor phenotype has been associated with highly aggressive tumors, causing invasion and metastases and resistance to cell death. However, natural killer (NK), but not T cells were found to kill mHsp70-positive tumor cells after activation with a naturally occurring Hsp70 peptide (TKD) plus low dose IL-2 (TKD/IL-2). Safety and tolerability of ex vivo TKD/IL-2
stimulated, autologous NK cells has been demonstrated in patients with metastasized colorectal and non-small cell lung cancer (NSCLC) in a phase I clinical trial. Based on promising clinical results of the previous study, a phase II randomized clinical study was initiated in 2014. The primary objective of this multicenter proof-of-concept trial is to examine whether an adjuvant treatment of NSCLC patients after platinum-based radiochemotherapy (RCTx) with TKD/IL-2 activated, autologous NK cells is clinically effective. As a mHsp70-positive tumor phenotype is associated with poor clinical outcome only mHsp70-positive tumor patients will be recruited into the trial. The primary endpoint of this study will be the comparison of the progression-free survival of patients treated with ex vivo activated NK cells compared to patients who were treated with RCTx alone. As secondary endpoints overall survival, toxicity, quality-of-life, and biological responses will be determined in both study groups.

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