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Treatment of advanced gastrointestinal cancer in a clinical phase I/II trial with genetically modified mesenchymal stem cells (gmMSC): A phase I clinical study

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Autologous gmMSC product Agenmestencel-T shows inherent ability to target tumors and express the therapeutic transgene HSV-TK under the control of the RANTES promoter *in situ*. Intravenously administered gmMSC migrate to tumors, where the promoter drives HSV-TK enzyme expression. Subsequently prodrug ganciclovir is administered intravenously. In tumors HSV-TK metabolizes ganciclovir to a cytotoxic product, which is taken up by tumor cells via gap junctions.

The phase I/II clinical trial TREAT-ME 1 was designed based on *in vivo* efficacy data and proof-of-concept in mice. In the completed phase I part, 6 advanced-stage gastrointestinal adenocarcinoma patients were treated: 3 CRC, 2 pancreatic, 1 CCC. gmMSC were administered in a low (3 patients; $0.5x10^6$ cells/kg-BW/week) or a high (3 patients; 10^6 cells/kg-BW/week) dose per week for 3 weeks, each followed by ganciclovir administration on days 3, 4 and 5.

The treatment was safe and tolerable in all patients. No related adverse or serious adverse events with CTC-AE grade 3-5 toxicity and no signs of clinically significant negative trends were recorded. The results indicate a decline of elevated liver enzymes and cholestasis parameters, due to the liver involvement, in chronological correlation to the therapy. The effect was not sustained after end of the treatment and might require repeated doses. According to RECIST (1.1) 4/6 patients showed stable disease at 3 months follow-up, 2/6 progressive disease. 1/6 was in sustained SD (>5 months). 2/6 patients had stable clinical condition.

This is the first reported clinical trial with gmMSC and the first report of MSC application in oncology. It shows that gmMSC are a viable, safe and promising therapeutic modality. The currently running phase II part evaluates the safety, tolerability and efficacy of Agenmestencel-T in 10 patients. A new phase I trial will start in 2016 to evaluate the use of donor-derived allogeneic gmMSC for tumor therapy.

Biography:

Dr. Günther has more than 20 years of experience in clinical hematology and oncology and worked for 6 years as QP, head of quality control and medical director at a public German stem cell/cord blood bank. Here she worked in the field of stem cell and tissue procurement, donor testing, characterization of cell products, and their application to the patient. She was especially involved in the clinical development and licensing of a cord blood product for the use in malignant diseases. In 2008 Dr. Günther joined apceth as the company´s managing director.