8 Summary

Treatment monitoring of CC-531 adenocarcinoma in the liver of WAG/RIJ rats by magnetic resonance imaging (MRI): A long-term trial

The dependancy of the antitumor effect of 5-fluorouracil (5-FU) from different applications was investigated in a long-term trial using a standardized experimental liver tumor model.
The aim of the present study was to improve the treatment of liver metastases from humane colorectal carcinoma.

To induce liver tumors 5 - 8 x 10^5 CC-531 adenocarcinoma cells were implanted into the liver of male WAG/RIJ rats.
5-FU was given directly or encapsulated in SUV-PEG liposomes (5-FU-SUV-PEG) with or without embolizate Spherex® either via the hepatic artery or the tail vein. Groups treated with Spherex®, empty SUV-PEG liposomes, SUV-PEG in combination with Spherex® and an untreated group served as control groups.
Before and every seven days after single treatment tumor bearing animals were examined with dynamic MR imaging to determine volume, growth and perfusion of the tumors. Serum parameters and the body weight were examined to evaluate toxic side effects of the therapy. The animals were sacrificed after reaching a tumor volume of more than 3500 µl, as determined by MR volumetry. The time between treatment and euthanasia was defined as survival time.
The different treatment and control groups were compared with respect to tumor growth and contrast agent kinetics in dynamic MR imaging. Results were correlated to histological findings of Hematoxylin-Eosin stained sections of the tumors.

A tumor regression could be observed in the first 14 days after intraarterial application of 5-FU-SUV-PEG-liposomes and embolizate Spherex®. The subsequent tumor growth in this group was delayed in comparison to all other groups and led to the longest median survival time of 8 weeks. The group treated with 5-FU-SUV-PEG i.a. showed different responses leading to reduced tumor volumes between 1 and 3 weeks followed by a tumor growth that started undelayed after regression. The mean survival time was 6 weeks. In both groups the tumor volume was reduced by 30 % in the first week after treatment. There was no significant difference in the duration of response between both groups. In each of these two groups one animal exhibited a complete response.
A signal reduction in dynamic MR imaging was seen only in the two successful treated groups in the first week after treatment. It was interpreted as a sign of temporary disturbed tumor perfusion. Mean survival times of all other treatment and control groups was 2 or 3 weeks. No reaction could be observed with MRI after therapy.

The ASAT, ALATand LDH levels which were increased before treatment returned to basic values within one week except for the untreated control group.
No dramatic reduction of body weight was seen in any of the groups.
The results of the dynamic MR imaging correlated well to the histological findings. There were no differences in the extent of necrotic areas in the various groups, because all animals showed advanced tumor growth and a similiar signal behavior in dynamic MR imaging at the time of euthanasia. At both animals with complete response a scar was found in the liver.

The results of this study correlate with former pharmacological studies in which 5-FU and it`s metabolite fluorodeoxyuridine (FUDR) were determined in several organs including liver and tumor tissue with HPLC techniques. Since 5-FU was applied identical to the presented study our results confirm the prognostic value of the determination of FUDR as effective, intracellular metabolite of 5-FU. These experiments show the effectiveness of liposomal encapsulated cytostatic agent 5-FU who led in combination with the embolizate Spherex® to a dramatic, selective accumulation of the therapeutic agent in tumor tissue and a temporary tumor regression after single treatment.

Based upon these findings we suggest further clinical testing (Trial I/II). Sequence therapy may further improve the treatment of humane liver metastases from colorectal carcinoma with longer lasting tumor reduction and prolonged survival of patients.