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Experimental examination of the MMP-inhibitor actinonin ex vivo and in vivo in a rat liver tumour model

According to the contemporary knowledge, matrix metalloproteinases (MMPs) play a decisive role in the metastatic spread of malignant tumours to the liver. MMPs are enzymes, which are responsible for the degradation of the extracellular matrix and are therefore very important tools in tumour progression, -invasion and metastatic spread. In the colorectal carcinoma (in humans) an increased expression of MMP -2 and -9 in the primary tumour is associated with an increased hepatic metastasis. Synthetic MMP-inhibitors are able to block the proteolytic activity of these enzymes. Consequently, MMP-inhibitors represent a potential therapeutic principle in oncology.

In the present study the synthetic MMP-inhibitor actinonin was examined for his effectiveness on the metastatic spread of CC 531 tumour cells ex vivo (matrigel invasion assay) and in vivo (rat liver tumour model).

For the ex vivo test transwell filters were coated with matrigel. The matrigel-coated filters were filled with CC 531 cells, after which actinonin was added (in 10% ethanol/saline). After incubation, fixation and staining, the analysis took place by counting the amount of cells which diffused through the matrigel.

Referring to the question, if the MMP-inhibitor actinonin decreased the invasion of CC 531 tumour cells ex vivo it showed, that the number of invading cells decreased with increasing actinonin concentration and stagnated at 100 µg / ml with 28,4 %. This means, that actinonin decreased the tumour cell invasion of CC 531 cells by 71,6 %.

To test the MMP-inhibitor in vivo the rat liver tumour model was used. WAG rats (n = 14) were injected with CC 531 cells via the intraportal vein. Group I (n = 8) was treated with actinonin, group II (n = 6) with a vehicle solution (NaCl, 0,9 %) for the duration of 5 days starting on the day of tumour implantation. Analysis took place 14 days after tumour implantation using the tumour replacement model as well as documenting the liver weight.

Referring to the question, if the MMP-inhibitor actinonin decreased the metastatic rate and / or the growth of hepatic metastases of portal venous injected CC 531 cells in vivo, it showed an arithmetic mean of 6,88 % for group I and 52,50 % for group II for tumour tissue compared to

the whole liver volume. Also noted was a difference in liver weight between the two groups, for group I 4,12 % and for group II 6,33 % as arithmetic mean.

This study shows the advantages of the MMP-inhibitor actinonin using a suitable in vivo rat liver tumour model, therefore representing a promising potential oncological therapy of malignant hepatic metastases of colorectal carcinoma.