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The Immunomodulatory Impact of Interferon Alpha in Combination with Chemoradiation of Pancreatic Adenocarcinoma (CapRI)

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Data from a phase II trial combining chemoradiotherapy with IFN-α (CapRI scheme) for adjuvant treatment of pancreatic carcinoma are very encouraging. Hypothesizing that IFN-α is the agent which significantly improves radiochemotherapy this work focuses on the immunomodulatory effect of IFN-α in this regimen.

Eight human ductal pancreatic carcinoma cell lines were treated with the CapRI scheme (5-Fluorouracil, Cisplatin, IFN-α and radiation). Peripheral blood lymphocytes, NK and T cells were preincubated with 1,000 U/ml IFN-α over 24 hours and tested in cytotoxicity assays against these cell lines. The mechanism of apoptosis induction was investigated, as well as the direct effect of IFN-α on pancreatic carcinoma cells regarding their immunogenicity and the influence on the DNA binding activity of the nuclear transcription factor NF-κB.

The results show an increase in cytotoxic activity of peripheral blood cells after IFN-α treatment from 12.5% to 34.3% ($p<0.05$). This cytotoxicity was NK cell mediated as shown after depletion of T cells (T cells 4% lysis, NK cells 42.7% lysis) and mediated by Fas-induced apoptosis as by perforin release. Pretreatment of tumor cells with 5-FU and combinations showed a significant increase in the susceptibility of tumor cells against NK cells (untreated tumor cells 34.3%, CapRI scheme 69.1%). While there is no significant difference between the whole CapRI scheme and chemoradiotherapy regarding cell proliferation rate and apoptosis induction, the cytotoxic effect of IFN-α stimulated lymphocytes against CapRI-treated pancreatic carcinoma cells is significantly higher than the

effect of unstimulated lymphocytes against chemoradiotreated cells (CapRI scheme -120.3%, chemoradiotherapy -75.2%, p=0.0001).

IFN-α alone was able to increase the immunogenicity of the pancreatic carcinoma cell lines through the increase of the mean expression of MHC class I in a significant manner, making the cells more susceptible to T cell cytotoxicity. In selected pancreatic carcinoma cell lines IFN-α might inhibit the DNA-binding activity of the nuclear transcription factor NF-κB.

IFN-α activates NK cells against pancreatic carcinoma cells and 5-FU treatment makes tumor cells more susceptible. These mechanisms may be responsible for the improved clinical outcome of CapRI.