

Combination chemotherapy with gemcitabine and biotherapy with opioid growth factor (OGF) enhances the growth inhibition of pancreatic adenocarcinoma

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Abstract Gemcitabine is the standard of care for advanced pancreatic neoplasia, and exerts its effect through inhibition of DNA synthesis. However, gemcitabine has limited survival benefits. Opioid growth factor (OGF) is an autocrine-produced peptide that interacts with the nuclear receptor, OGF_r, to inhibit cell proliferation but is not cytotoxic or apoptotic. The present study was designed to examine whether a combination of chemotherapy with gemcitabine and biotherapy with OGF is more effective than either agent alone in inhibiting pancreatic cancer growth *in vitro* and *in vivo*. The combination of OGF (10^{-6} M) and gemcitabine (10^{-8} M) reduced MIA PaCa-2 cell number from control levels by 46% within 48 h, and resulted in a growth inhibition greater than that of the individual compounds. OGF in combination with 5-fluorouracil also depressed cell growth more than either agent alone. The action of OGF, but not gemcitabine, was mediated by a naloxone-sensitive receptor, and was completely reversible. OGF, but no other endogenous or exogenous opioids, altered pancreatic cancer growth in tissue culture. The combination of OGF and gemcitabine also repressed the growth of another pancreatic cancer cell line, PANC-1. MIA PaCa-2 cells transplanted into athymic mice received 10 mg/kg OGF daily, 120 mg/kg gemcitabine every 3 days; 10 mg/kg OGF daily and 120 mg/kg gemcitabine every 3rd day, or 0.1 ml of sterile saline daily. Tumor incidence, and latency times to tumor appearance, of mice receiving combined therapy with OGF and gemcitabine, were significantly decreased from those of the control, OGF, and gemcitabine groups. Tumor volumes in the OGF, gemcitabine, and OGF/gemcitabine groups were markedly decreased from controls beginning on days 14, 12, and 8, respectively, after tumor cell inoculation. Tumor weight and tumor volume were reduced from control levels by 36–85% in the OGF and/or gemcitabine groups on day 45 (date of termination), and the group of mice exposed to a combination of OGF and gemcitabine had decreases in tumor size of 70% and 63% from the OGF or the gemcitabine alone groups, respectively. This preclinical evidence shows that combined chemotherapy (e.g. gemcitabine) and biotherapy (OGF) provides an enhanced therapeutic benefit for pancreatic cancer.

Keywords [Met⁵]-enkephalin - Opioid growth factor - Neoplasia - Gemcitabine - 5-Fluorouracil - Pancreatic cancer