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Pancreas

Pharmacologic Ascorbate Reduces Radiation-Induced Normal Tissue Toxicity and Enhances Tumour Radiosensitisation in Pancreatic Cancer.

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ABSTRACT

Chemoradiation therapy is the mainstay for treatment of locally advanced, borderline resectable pancreatic cancer. Pharmacologic ascorbate (P-AscH-, i.e., intravenous infusions of ascorbic acid, vitamin C), but not oral ascorbate, produces high plasma concentrations capable of selective cytotoxicity to tumour cells. In doses achievable in humans, P-AscH- decreases the viability and proliferative capacity of pancreatic cancer via a hydrogen peroxide (H_2O_2)-mediated mechanism. In this study, we demonstrate that P-AscH- radiosensitises pancreatic cancer cells but inhibits radiation-induced damage to normal cells.

Specifically, radiation-induced decreases in clonogenic survival and double-stranded DNA breaks in tumour cells, but not in normal cells, were enhanced by P-AscH-, while radiation-induced intestinal damage, collagen deposition, and oxidative stress were also reduced with P-AscH- in normal tissue. We also report on our first-in-human phase I trial that infused P-AscH- during the radiotherapy "beam on". Specifically, treatment with P-AscH- increased median overall survival compared with our institutional average (21.7 vs. 12.7 months, $P = 0.08$) and the E4201 trial (21.7 vs. 11.1 months). Progression-free survival in P-AscH-treated subjects was also greater than our institutional average (13.7 vs. 4.6 months, $P < 0.05$) and the E4201 trial (6.0 months).

Results indicated that P-AscH- in combination with gemcitabine and radiotherapy for locally advanced pancreatic adenocarcinoma is safe and well tolerated with suggestions of efficacy. Because of the potential effect size and minimal toxicity, our findings suggest that investigation of P-AscH- efficacy is warranted in a phase II clinical trial.

SIGNIFICANCE

These findings demonstrate that pharmacologic ascorbate enhances pancreatic tumour cell radiation cytotoxicity in addition to offering potential protection from radiation damage in normal surrounding tissue, making it an optimal agent for improving treatment of locally advanced pancreatic adenocarcinoma.