**Nrf2 in pancreatic cancer chemotherapy response and the use of brusatol as a chemotherapeutic agent.**

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Gemcitabine resistance in pancreatic cancer has been reported to be enhanced by the Nrf2 antioxidant pathway. Nrf2 induces expression of NQO1. Brusatol, an Nrf2 inhibitor, possess anti-cancer properties with low general toxicity. This study aimed to investigate the role of Nrf2 in treatment response and to determine if brusatol is a viable chemotherapeutic agent.

Microarrays from 195 patients randomized to chemotherapy in the ESPAC-3 trial (plus controls from ESPAC-1) were stained for expression of NQO1. Cytoplasmic NQO1 levels were categorised as high or low and groups compared using Kaplan-Meier curves, log-rank tests, and Cox proportional hazards models. Median survival following gemcitabine treatment was 13.5 (95% CI = 9.9 to 16.8) months for those with low NQO1 vs 24.1 (95% CI = 15.5 to 28.8) months for those with high NQO1 expression (P=.01). For the 5-fluorouracil group, median survival was 13.9 (95% CI = 10.7 to 19.5) and 21.8 (95% CI = 16.9 to 25.7) months for those with low and high NQO1 expression, respectively (P=.07). NQO1 levels were not predictive of survival for the 27 patients of the observation group (P=.69). Nrf2 and NQO1 levels were either reduced or unchanged following exposure of PDAC cell lines (MiaPaca2, Suit2, Panc1) to gemcitabine. Brusatol reduced Nrf2 levels and totally inhibited detectable protein synthesis.

Gemcitabine treatment appears to reduce Nrf2 and NQO1 levels in cell lines, however high NQO1 levels correspond to better outcome following gemcitabine treatment in patients. Ongoing work will determine if the protein synthesis inhibition associated with brusatol is a consequence of oxidative stress due to Nrf2 depletion. In vitro and in vivo models will explore the use of brusatol for chemotherapeutic benefit.