Effects of Gemcitabine/Nab-Paclitaxel and DMAPT in PDAC Cachexia *in vivo* and *in vitro*

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Cachexia is the involuntary wasting of skeletal muscle and adipose tissue, affecting over 80% of patients with pancreatic ductal adenocarcinoma (PDAC). Gemcitabine and nab-paclitaxel (GemNP) combination are commonly given as first-line treatments for PDAC. Data from our lab showed GemNP reduced tumor growth and prevented muscle and fat wasting. Dimethylaminoparthenolide (DMAPT), a small molecule inhibitor, prevented muscle wasting and prolonged survival in a genetic murine model of breast cancer. It has yet to determine if GemNP in combination with DMAPT can improve indices of cachexia and overall survival. Therefore, I hypothesize that GemNP in combination with DMAPT will improve indices of cachexia and overall survival in a murine model of pancreatic cancer.

Male 10-week-old C57BL/6J mice underwent orthotopic injection of $5x10^4$ KPC cells or SHAM surgery. Mice were randomly assigned to 1 of 4 groups (N=10/group): SHAM+Vehicle, KPC+Vehicle, KPC+GemNP, KPC+GemNP+DMAPT. Gemcitabine (120mg/kg) and Nab-paclitaxel (10mg/kg) were injected intraperitoneally starting on day 4 and continued every 6 days. DMAPT (100mg/kg) was administered by gavage Monday-Friday. To determine the role of GemNP and DMAPT *in vitro*, KPC cells were treated with GemNP and/or DMAPT and cell viability evaluated. Additionally, we treated myotubes with GemNP with/without DMAPT to assess myotube diameter in an established KPC conditioned media.

In KPC mice, GemNP (24.4days) increased survival compared to Vehicle (16.8days, p=.0007). However, the combination GemNP+DMAPT did not extend survival over GemNP alone (25.4days, p=.693). Tumor mass was similar between all groups (p=0.411). Interestingly, at the time of sacrifice, all KPC treated mice independent of treatment had similar reduction in adipose tissue and muscle mass compared to SHAM.

In conclusion, the addition of DMAPT to GemNP did not extend survival over GemNP alone in an aggressive pancreatic tumor cell line. Future studies should determine if less aggressive tumor cell lines might benefit from GemNP and DMAPT.