ALDH Stem Cells are Predictive of Survival in Patients with Pancreatic Adenocarcinoma Treated with Adjuvant Chemoradiation

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Background
Tumor initiating (stem) cells have been associated with decreased survival and treatment resistance in pancreatic adenocarcinoma. Aldehyde dehydrogenase (ALDH) activity has identified normal and cancer stem cells in pancreas cancer. We investigated the role of ALDH in identifying local control and survival in patients treated with chemoradiation (CRT) following pancreatectomy.
Hypothesis
Patients whose pancreas cancer specimens demonstrate increased ALDH activity will have higher treatment resistance to adjuvant chemoradiation and, subsequently, have a lower survival.
Methods
Tissue microarrays were generated using pancreatectomy specimens from our institution. Tissues were stained for ALDH1 and reviewed by two expert pancreatic cancer pathologists who were blinded to patient outcomes. Physician documentation and radiology reports were used to generate patient follow-up information. Patients with follow-up data of less than 2 months were excluded from local failure free survival (LFFS) analysis. Kaplan-Meier curves were generated for LFFS, distant metastasis free survival (DMFS), and overall survival (OS) using SPSS software.
Results
In a previous study, using a tissue microarray of 269 patients with resected pancreatic tumors, we found that ALDH expression was associated with worse OS (Rasheed, JNCI 2009). From this original cohort, adjuvant treatment information was available for 88 patients with ALDH- tumors (49.1%) and 41 patients with ALDH+ tumors (45.6%) patients. In patients treated with adjuvant CRT, median overall survival was superior in the ALDH- cohort vs the ALDH+ cohort, 26.3 months vs 18.2 months, p=0.011, particularly in R0 and N1 patients. Further, in patients treated with adjuvant CRT, ALDH- patients had statistically greater LFFS and DMFS than their ALDH+ counterparts (see table). Within the ALDH- cohort, patients treated with adjuvant CRT had a longer LFFS (45.9 months vs 7.4 months, p<0.001) and DMFS (27.8 months vs 4.7 months, p<0.001) than those not receiving CRT. Similar analysis was not possible in the ALDH+ cohort due to a limited number of patients that did not receive adjuvant CRT.
Discussion
This data suggests that adjuvant CRT is particularly efficacious in pancreatic adenocarcinoma not enriched with ALDH expressing stem cells. We are in the process of studying ALDH expression as a biomarker for predicting response to chemoradiation in patients with locally advanced pancreatic adenocarcinoma. Further pre-clinical studies will help elucidate the mechanisms of treatment resistance in ALDH expressing tumors and cells.

	ALDH Negative	**ALDH Positive**	**P-value**
OS – All Patients	18.1 months (n=177)	14.8 months (n=90)	P=0.026
OS – With Adjuvant CRT	26.3 months (n=69)	18.2 months (n=35)	P=0.011
OS – R0 With Adjuvant CRT	31.9 months (n=42)	21.7 months (n=23)	P=0.027
OS – R1 With Adjuvant CRT	17.9 months (n=27)	11.3 months (n=12)	P=0.181
OS – N0 with Adjuvant CRT	26.5 months (n=10)	29.9 months (n=7)	P=0.187
OS – N1 With Adjuvant CRT	25.1 months (n=59)	17.2 months (n=28)	P=0.024
LFFS – Current cohort	45.9 months (n=87)	18.9 months (n=41)	P=0.117
LFFS – With Adjuvant CRT	45.9 months (n=69)	21.0 months (n=35)	P=0.044
DMFS – Current cohort	25.1 months (n=87)	17.8 months (n=41)	P=0.025
DMFS – With Adjuvant CRT	27.8 months (n=69)	14.8 months (n=35)	P=0.002