Metabolic response of human prostate cancer post 17 AAG treatment in a mouse model

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Synopsis:

Hsp90 inhibitor 17AAG is being studies as a chemotherapy agent against prostate cancers. It has been shown to cause tumor growth arrest and partial shrinkage. Using total choline as a tumor proliferation surrogate maker, we compare the metabolic response of the hormone sensitive and resistant human prostate cancer CWR22 after 17AAG treatment. Differential responses of the two cancer lines shows that 17AAG can be a promising agent for the resistant line and that ^{1}H MRS is a sensitive technique for tumor monitoring.

Introduction:

17-allylamino-17-demethoxygeldanamycin (17AAG), an ansamycin antibiotic currently under Phase I clinical trial for anti-tumor activity, is an inhibitor of Hsp90 chaperone which regulates signaling proteins important for tumor cell progression [1, 2]. 17AAG inhibits the growth of a number of tumor cell lines and enhances tumor response to radiation. In this study we compared the response of the hormone sensitive and resistant human prostate cancer CWR22 and CRW22r lines to 17AAG using ^{1}H MRS.

Methods:

The hormone sensitive CWR22 human prostate cancer cells is a gift from Solit, et. al [2]. The hormone resistant line CWR22r was obtained from ATCC (ATCC, Manassas, VA). Tumors were transplanted subcutaneously (SC) in athymic nude mice flank using minced tumor tissue. Testosterone pellets were implanted s.c. one day prior to transplantation. 17AAG (100mg/kg) was administered i.p. at a tumor volume of approximately 500 mm^3. ^{1}H CSI was acquired before, 4 hours, 48 hours and 7 days post treatment. ^{1}H 3D CSI measurements were performed on a Bruker 4.7T Biospec scanner (Bruker Biospin MRI, Billerica, MA). A 200 MHz home-built 2-turn solenoid coil around the mouse flank tumor was used [3]. Water suppression was achieved by CHESS presaturation. Acquisition parameters of TR 1s, TE 75ms, FOV 32mm, 16x16 matrix size and 512 complex data points with a 2003 Hz spectral width were used. Total Choline was measured using the peak intensity at 3.2 ppm. SAGEIDL software package (GE Medical, Milwaukee, WI) was used for data processing.

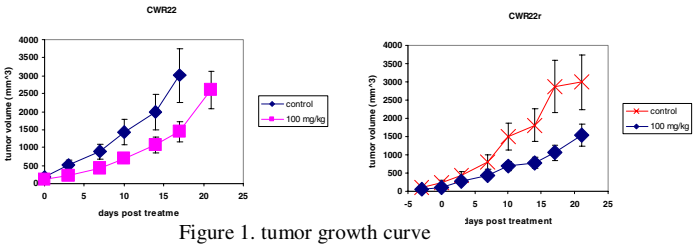

Figure 1. tumor growth curve

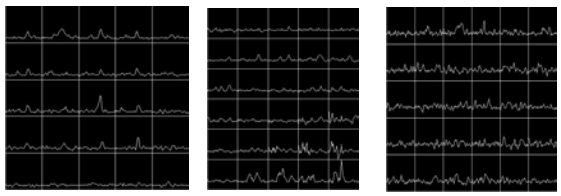

Figure 2. ^{1}H CSI grid plot. A). 0 hour B) 4 hour. C) 48 hour

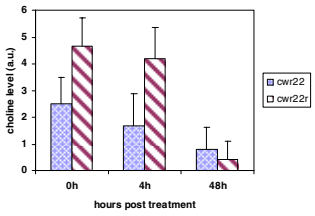

Figure 3. Relative choline levels

Results and Discussions:

Tumor doubling time (TDT) is found to be 4.5 ± 0.4 and 5.0 ± 0.4 days for CWR22 and CWR22r respectively in the control group. At the dose of 100 mg/kg, the growth delay is small but significant, Figure 1. Measured at 17 days, the treated mice have significantly smaller tumors than the untreated ones (P=0.016 and P=0.003 for CWR22 and CWR22r respectively). Treatment with 17AAG caused downregulation of AR and HER2 expression in the tumor at none toxic doses. Metabolic response of the tumors were detected using ^{1}H MRS. Figure 2 shows typical ^{1}H CSI spectra at pre-, 4 hours and 48 hours post 17AAG treatment. Relative total choline level shows that the hormone resistant CWR22r has almost twice the amount than the sensitive tumor CWR22, Figure 3. At 4 hours post treatment a slight decrease in total choline level is noticed for CWR22 (N=7), among which there is a complete reduction for 2 mice. The total choline level for CWR22r is almost unchanged at 4-hour, but had a dramatic decline at 48 hour with 5 of 7 mice having undetectable choline. Choline level for CWR22 also show further decrease at 48 hour. ^{1}H MRS in this study revealed that the human prostate tumor CWR22 and CWR22R had a favorable metabolic response to the new anti-cancer agent 17AAG even at a lower dose and the response is more pronounced for the resistant tumor offering a promising option for late stage prostate cancer [4]. This metabolic effect can be detected within 48 hours after treatment prior to tumor shrinkage and is therefore potentially an early tumor response predictor.

References:

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