P58 Docetaxel efficacy in prostate cancer is affected by testosterone; unraveling clinical observations

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Introduction & Objectives: Emerging data from the recent years have implicated an interplay between androgens and taxane treatment efficacy for metastatic prostate cancer. The STAMPEDE and CHAARTED trials suggest that docetaxel efficacy is greatly improved by the addition of androgen deprivation therapy (ADT) in hormone sensitive prostate cancer, while docetaxel treatment in the naïve setting has been shown to be ineffective. We sought to determine the impact of androgens and the androgen receptor (AR) pathway on the efficacy of docetaxel.

Materials & Methods: We studied the impact of testosterone on docetaxel efficacy in an in vivo model of castrate resistant prostate cancer (PC346-DCC-K; AR+/PSA+). To assess in vivo docetaxel accumulation we treated castrate and testosterone supplemented mice with docetaxel and isolated tumors after 3 days. Uptake competition between docetaxel and testosterone for OATP1B3 uptake was studied, by exposing HEK293T-OATP1B3 cells to C^{14}-docetaxel with or without testosterone. Tubulin stabilization by docetaxel was assessed by immunoblotting of acetylated α-tubulin. In vitro efficacy of docetaxel in the presence of androgens was assessed by cell viability assays. We performed a TUNEL staining on short-term docetaxel treated tumors, to identify apoptotic/necrotic cells.

Results: Testosterone supplementation greatly impacted docetaxel efficacy as all tumors progressed under docetaxel treatment, while we observed long-term tumor regression in castrate mice. Furthermore, docetaxel accumulation in tumors was reduced by ~40% in the presence of testosterone. We therefore studied uptake of docetaxel by the drugtransporter OATP1B3 in the presence of testosterone, since both are substrates for OATP1B3 and uptake competition could impair docetaxel uptake. Docetaxel uptake by OATP1B3 was reduced by 17% in the presence of testosterone. Furthermore, we identified a trend towards decreased tubulin stabilization by docetaxel in the presence of testosterone. Interestingly, long-term docetaxel induced tumor regression could be reversed by testosterone exposure. We hypothesized that AR pathway activation contributes to docetaxel resistance in prostate cancer. Indeed, docetaxel-induced apoptosis was strongly diminished in testosterone supplemented mice. Furthermore, in vitro data revealed that androgen exposure led to an increase in proliferative cells in the presence of docetaxel.

Conclusions: Overall, our study shows that taxane efficacy is negatively impacted by androgens in prostate cancer. Our study implies that in order to maximize docetaxel accumulation and to prevent AR mediated docetaxel resistance androgen levels need to be suppressed. These data also provides strong support for the continued use of antiandrogens during docetaxel treatment to enhance taxane efficacy for metastatic prostate cancer.