Targeting pain: A novel adjunct treatment to relieve BCG-immunotherapy induced lower urinary tract side effects

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Introduction. 70% of patients undergoing BCG immunotherapy for non-muscle invasive bladder cancer (NMIBC) experience lower urinary tract symptoms (LUTS) including bladder pain, that significantly reduce quality of life during treatment. In 7-20% of patients these side effects are so severe that they require cessation of therapy. Despite this, there is no standard treatment to ease NMIBC patient suffering and improve treatment adherence. Phenazopyridine is an FDA/TGA approved urinary tract analgesic that shows clinical efficacy in relieving LUTS in patients with urinary tract infection, however, it's utility in treating BCG-induced LUTS has yet to be determined.

AIMS. The aim of this study was to determine if phenazopyridine can reduce BCG-induced bladder hypersensitivity without impacting the efficacy of BCG in bladder cancer treatment.

METHODS. The impact of phenazopyridine (300μM) on bladder sensory nerve excitability in response to distension (50mmHg) was determined using an ex-vivo bladder afferent nerve recording technique. The effect of phenazopyridine (300μM) on the immune response to BCG was determined via flow cytometry of mouse bladder cells after 6 consecutive weeks of BCG ($1x10^7$ CFU), or BCG + Phenazopyridine (300μM) treatment. Impacts of phenazopyridine (3-300μM) on bladder cancer growth we determined *in-vitro* by analysis of MB49 bladder cancer cell line proliferation.

RESULTS. Our ex-vivo nerve recording experiments show phenazopyridine significantly attenuates bladder sensory signalling during distension ($P<0.001$, N=5/Group). BCG evoked significant increases in immune cell populations that were unchanged following co-administration of BCG with phenazopyridine, including the total numbers of infiltrating CD45+ immune cells ($P>0.05^{ns}$, N=10/Group) and immune cell subtypes including neutrophils, dendritic cells, macrophages, inflammatory monocytes, natural killer cells and CD4+ and CD8+ T cells. High (100-300μM), but not low (3-30μM) concentrations of phenazopyridine significantly inhibited bladder cancer cell growth ($P<0.001$, N=3).

DISCUSSION. This study shows that phenazopyridine can effectively reduce bladder sensory signalling without impacting the BCG-induced immune response necessary for cancer treatment or promoting bladder cancer cell growth. This study indicates phenazopyridine may be a useful therapeutic to prevent BCG-induced bladder side effects in NMIBC patients to improve quality of life and oncological outcomes.