Abstract 1880: In vitro and in vivo investigations of anlotinib in bladder cancer treatment

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Background:
Bladder cancer is one of the most common malignancies in the urinary system. Fibroblast growth factor receptor 3 (FGFR3) is the most common alteration gene in bladder cancer, occurring in approximately 60% of non-metastatic bladder cancer and 20% of metastatic bladder cancer [1]. Anlotinib is a potent oral, multi-target tyrosine kinase inhibitor with a favorable safety profile, mainly targeting vascular endothelial growth factor receptor (VEGFR), FGFR, platelet-derived growth factor receptors, and c-kit. This study aims to investigate the anti-cancer effects of anlotinib in bladder cancer cells compared with FGFR3 inhibitor erdafitinib in vitro and in vivo.

Methods:
MTT, colony formation, and Transwell assays were performed to confirm the effects of anlotinib and erdafitinib on the proliferation, migration, and invasion of bladder cancer cells (SW780 and UMUC14). The levels of the protein and mRNA were examined by Western blotting, RNA-seq, and RT-qPCR. Finally, mice with palpable xenografts were treated either with 15 mg/kg anlotinib or erdafitinib for 8 days before they were sacrificed for measuring the sizes and weights of the tumors.

Results:
To assess the roles of anlotinib in bladder cancer, we treated SW780 cell line which had FGFR3-BALAP2L1 fusion rearrangement and UMUC14 cell line which had a S249C mutation in FGFR3 with DMSO, anlotinib, and erdafitinib. Anlotinib inhibits tumor cell proliferation (Figure 1A-B), migration (Figure 1C-D), and invasion (Figure 1E-F) of SW780 and UMUC14. Compared with erdafitinib, anlotinib showed stronger in vitro anti-tumor efficacy especially in SW780 cell line with FGFR3-BALAP2L1 fusion mutation. Mechanistically, anlotinib and erdafitinib inhibited the phosphorylation of Erk1/2 (p-Erk1/2) and AKT (p-AKT), while only anlotinib inhibited the expression of VEGF2 as demonstrated by Western blotting (Figure 2A) and RT-PCR assays (Figure 2B). In addition, the in vivo data from xenografts also supported that anlotinib could significantly repress tumor growth with FGFR3 fusion mutation, and the efficacy was superior to erdafitinib (Figure 3). Anlotinib could repress the proliferation, migration, and invasion of bladder cancer cells by inhibiting the phosphorylation of Erk1/2 and AKT, and the suppression of VEGF2 expression. The effect and efficacy of anlotinib is superior to erdafitinib against bladder cells with FGFR3 fusion rearrangement in vitro and in vivo. Therefore, anlotinib might be a potential novel targeted agent to treat bladder cancer patients with FGFR3 fusion mutations, and clinical trials are needed for further investigation.

Figure 1. Inhibition of cell proliferation (A-B), migration (C-D) and invasion (E-F) with anlotinib and erdafitinib.

Figure 2. Effect of anlotinib and erdafitinib on the expression of VEGF2, Erk1/2 and AKT.

Figure 3. Anti-cancer effects of anlotinib in SW780-derived xenograft model.

Conclusions: Anlotinib could repress the proliferation, migration and invasion of bladder cancer cells by inhibiting the phosphorylation of Erk1/2 and AKT, and the suppression of VEGF2 expression. The effect and efficacy of anlotinib is superior to erdafitinib against bladder cells with FGFR3 fusion rearrangement in vitro and in vivo. Therefore, anlotinib might be a potential novel targeted agent to treat the bladder cancer patients with FGFR3 fusion mutations, and clinical trials are needed for further investigation.