BLADDER CANCER

Aurora kinase inhibitors light up the therapeutic horizon in bladder cancer

Nonsurgical treatments for bladder cancer have been stagnating, with few advances in recent years. Now, a new study published in *Clinical Cancer Research* has provided the first preclinical evaluation of Aurora kinase inhibitors as a potential treatment for bladder cancer.

Aurora kinases are a family of serine/threonine kinases essential for cell cycle progression during the G2 and M phases. Overexpression of Aurora A and B has been shown to correlate with pathological and clinical parameters in bladder cancer and Aurora kinase inhibitors—such as the orally active MLN8237—have, therefore, been proposed as potential therapies.

Zhou *et al.* used gene expression analysis to show that 155 genes were dysregulated in human bladder cancer tissue, 13 of which encoded components of the mitotic spindle checkpoint, including Aurora A and B. As Aurora A has previously demonstrated a role in mitotic progression, the team then focused on Aurora A as a potential therapeutic target.

Beginning with cell culture studies, they treated the human urothelial carcinoma cell lines T24 and UM-UC-3 with MLN8237, with the benign urothelial papilloma cell line RT4 as a control, observing a loss of

phospho-Aurora A at the mitotic spindle and a dose-dependent reduction in Aurora A phosphorylation compared with baseline levels. When the researchers went on to assess cell cycle dynamics using flow cytometry, they showed that MLN8237 treatment for 48 h arrested the cell cycle, with an increase in 4N DNA (a marker of G2/M arrest) from 9% to 72% in T24 cells, 10% to 84% in UM-UC-3 cells and 22% to 92% in RT4 cells. Microscopy revealed mitotic arrest, rounded cell morphology and disruption of mitotic spindle formation. The team went on to quantify cell viability and found that MLN8237 was more potent in the cancerous cell lines T24 and UM-UC-3 (IC_{50} 31 nM and 45 nM respectively), than in the benign RT4 cells (IC_{50} 120 nM).

The group used a T24 xenograft model to assess *in vivo* activity, with mice administered 30 mg/kg MLN8237 orally five times weekly for 4 weeks. Tumours in mice treated with MLN8237 showed no significant growth during the 4-week regimen, with complete growth arrest; however, untreated control mice exhibited a quadrupling in tumour size within 2 weeks of the study initiation. Harvested tumours showed decreased cellularity and regions of fibrosis and cell death in MLN8237-treated tumours compared with controls.

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Finally, Zhou *et al.* investigated whether MLN8237 could be used in combination with current bladder cancer treatments paclitaxel or gemcitabine. Combination treatment with MLN8237 and either paclitaxel or gemcitabine synergistically reduced cell viability when compared with either drug alone. “Sequential application of MLN8237 and conventional chemotherapeutic agents ... enhanced the effects of MLN8237 and may represent a novel therapeutic avenue in this disease”, first author Ning Zhou told *Nature Reviews Urology*. “There is a clinical urgency for better understanding of molecular pathways that underlie bladder cancer pathogenesis that can be targeted pharmacologically. In particular, we feel that the mitotic spindle checkpoint warrants further investigation as a potential therapeutic target”.

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Original article Zhou, N. *et al.* The investigational Aurora kinase A inhibitor MLN8237 induces defects in cell viability and cell cycle progression in bladder cancer cells *in vitro* and *in vivo*. *Clin. Cancer Res.* doi:10.1158/1078-0432.CCR-12-2383