World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:19, No:08, 2025

Evaluating Therapeutic Efficacy of Intravesical Xenogeneic Urothelial Cell Treatment Alone and in Combination with Chemotherapy or Immune Checkpoint Inhibitors in a Mouse Non-Muscle-Invasive Bladder Cancer Model

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Abstract : Intravesical BCG is the gold-standard therapy for high risk non-muscle invasive bladder cancer (NMIBC) after TURBT, but if not responsive to BCG, these BCG unresponsive patients face cystectomy that causes morbidity and comes with a morality risk. To provide the bladder sparing options for patients with BCG-unresponsive NMIBC, several new treatments have been developed to salvage the bladders and prevent progression to muscle invasive or metastatic, but however, most approved or developed treatments still fail in a significant proportion of patients without long term success. Thus more treatment options and the combination of different therapeutic modalities are urgently needed to change the outcomes. Xenogeneic rejection has been proposed to a mechanism of action to induce anti-tumor immunity for the treatment of cancers due to the similarities between rejection mechanism to xenoantigens (proteins, glycans and lipids) and anti-tumor immunities to tumor specific antigens (neoantigens, tumor associated carbohydrates and lipids). Xenogeneic urothelial cells (XUC) of porcine origin have been shown to induce anti-tumor immune responses to inhibit bladder tumor progression in mouse bladder cancer models. To further demonstrate the efficacy of the distinct intravesical XUC treatment in NMIBC, and the combined effects with chemotherapy and immune checkpoint inhibitors (ICIs) as a alternate therapeutic option, this study investigated the therapeutic effects and mechanisms of intravesical XUC immunotherapy in an orthotopic mouse immune competent model of NMIBC, generated from a mouse bladder cancer cell line. We found that the tumor progression was inhibited by intravescial XUC treatment and there was a synergy between intravesical XUC with intravesical chemotherapeutic agent, gemcitabine or systemic ICI, anti-PD1 antibody treatment. The cancer cell proliferation was decreased but the cell death was increased by the intravecisal XUC treatment. Most importantly, the mechanisms of action of intravesical XUC immunotherapy were found to be linked to enhanced infiltration of CD4+ and CD8+ T-cell as well as NK cells, but decreased presence of myeloid immunosuppressive cells in XUC treated tumors. The increased stimulation of immune cells of XUC treated mice to xenogeneic urothelial cells and mouse bladder cancer cells in immune cell proliferation and cytokine secretion were observed both as a monotherapy and in combination with intravesical gemcitabine or systemic anti PD-L1 treatment. In sum, we identified the effects of intravesical XUC treatment in monotherapy and combined therapy on tumor progression and its cellular and molecular events related to immune activation to understand the anti-tumoral mechanisms behind intravesical XUC immunotherapy for NMIBC. These results contribute to the understanding of the mechanisms behind successful xenogeneic cell immunotherapy against NMIBC and characterize a novel therapeutic approach with a new xenogeneic cell modality for BCG-unresponsive NMIBC.

Keywords : xenoantigen, neoantigen, rejection, immunity
Conference Title : ICTII 2025 : International Conference on Tumor Immunology and Immunotherapy
Conference Location : Vancouver, Canada
Conference Dates : August 05-06, 2025