In Vivo Evaluation of a Biomimetic Polymer-Doxorubicin Conjugate for Cancer Therapy

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Abstract

This poster will describe a novel polymer pro-drug platform designed for conjugation and delivery of chemotherapeutics. Specifically, polymer pro-drugs were prepared from functional polymer zwitterions and doxorubicin (DOX), and evaluated *in vivo* to assess toxicological, pharmacokinetic and therapeutic properties. The biocompatible polymer scaffold (PolyMPC) consists of zwitterionic phosphorylcholine pendent groups, which mimic the natural hydrophilic moieties of phospholipids in cell membranes, and hydrazone linkages that allow for pH-triggered release of DOX. PolyMPC-DOX pro-drugs were isolated as dry solids using a facile strategy that allows for precise control of molecular weight and DOX incorporation. *In vivo* toxicity of PolyMPC and PolyMPC-DOX was assessed in a murine model. The maximum tolerated dose of the pro-drug was five times greater than that of free DOX, while PolyMPC alone exhibited no toxicity even at a dose of 800 mg/kg. A pharmacokinetic study in tumor-bearing mice demonstrated a significant increase in circulation half-life of conjugated DOX ($t_{1/2}$=2 hours) compared to free DOX ($t_{1/2}$=15 minutes), with conjugated DOX detectable in blood serum for longer than 24 hours. This pronounced enhancement in circulation time was attributed to the macromolecular scaffold, which precludes rapid renal clearance compared to native DOX. Examination of mice given PolyMPC-DOX five days after injection in the PK study showed a three-fold increase of drug accumulated in tumor tissue compared to that of mice treated with free DOX and drug accumulation in off-target organs was reduced for mice given DOX conjugate. The therapeutic efficacy of the PolyMPC-DOX conjugates was then assessed in an orthotopic murine breast cancer model. The treatment group given PolyMPC-DOX exhibited a two-fold increase in overall survival and a significant reduction in average tumor volume compared to the free DOX and saline control groups. A study evaluating the therapeutic efficacy of PolyMPC-DOX in a human ovarian xenograft tumor model is ongoing.