Nanospheric Chemotherapeutic and Chemoprotective Agents

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Statement of Purpose: To evaluate the potential of tyrosine-derived nanospheres as drug delivery vehicles: anti-tumor activity, pharmacokinetics and biodistribution of paclitaxel-loaded nanospheres in human breast tumor xenograft in mouse model. Novel drug delivery strategies can play a pivotal role in improving the parenteral delivery of pharmaceuticals with poor bioavailability by improving their stability, circulation times in the body, and permeability through cell membranes, while reducing their toxicity.[1] Paclitaxel (Taxol®) is used widely for the treatment of breast and other types of solid tumor cancers.[2] Paclitaxel (PTX) is only sparingly soluble in water and so intravenous administration depends on the use of Cremophor® EL (polyethoxylated castor oil) to obtain a sufficiently concentrated solution. Unfortunately, use of Cremophor (CrEL) increases patient toxicity and can lead to clinically important adverse effects, including acute hypersensitivity reactions and peripheral neuropathy.[3]

To improve the therapeutic potency of PTX and to overcome the toxicities associated with PTX-CrEL we have developed a nanosphere system based on biodegradable and non-cytotoxic copolymers (Figure 1).[4,5] The ABA-type triblock copolymers consist of poly(ethylene glycol) A-blocks and hydrophobic low molecular weight polyarylates B-blocks made of desaminotryosyl-tyrosine alkyl esters (DTR) and diacids.[4,5] These copolymers self-assemble into nanospheres (NSP) with hydrodynamic diameters of ca. 70 nm and form stable complexes with a wide variety of hydrophobic therapeutics.[5]

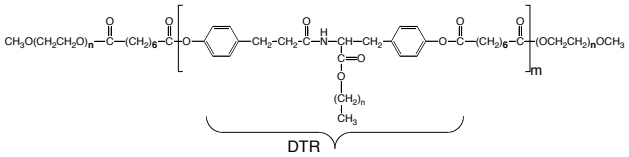

Figure 1. Tyrosine-derived triblock copolymers.

Methods: The triblock copolymers and paclitaxel-loaded nanospheres (PTX-NSP) were prepared and characterized as previously described using ^{1}H NMR, DSC, GPC, HPLC and DLS techniques.[4,5] Cremophor (CrEL) formulations were prepared by dissolving PTX in CrEL:PBS (50:50 v/v) to reduce the lethal effect of neat CrEL on mice. The *in vitro* cellular activities of PTX-NSP and PTX-CrEL were determined in the epithelial human breast adenocarcinoma cell line, MDA-MB-231, using an MTS assay. *In vivo* toxicity and anti-tumor efficacy on PTX-NSP and PTX-CrEL formulations were assessed in NCR nu/nu control mice and mice bearing subcutaneous MDA-MB-231 breast cancer xenografts. NSP alone and CrEL alone were used as a control. Test formulations were administered intraperitoneally using a q5dx4 administration schedule.

Results: In vitro release kinetics of PTX-NSP are strongly dependent upon the pH: after 72 hrs 72% of paclitaxel is released at pH 5.5 compared to just 52% at pH 7.4. The enhanced drug release at pH 5.5, which is typical of extracellular pH of solid tumors, is expected to have an increase therapeutic advantage of our nanospheres. No decrease of the cell metabolic activity of MDA-MB-231 cells was detected after exposure to NSP alone, compared to an 80% decrease in cell viability when treated with CrEL alone, demonstrating that NSP do not induce acute cytotoxicity. In addition, NSP provided substantially enhanced delivery (2.2-fold, $p < 0.05$) of PTX to MDA-MB-231 cells compared to CrEL at the equivalent drug concentrations. The NSP-PTX (5 to 35 mg/kg) did not exhibit any in vivo toxicity based on the absence of change in weight and behavior, skin irritation and sensitization in any of the treated groups after 4 treatments. In contrast, PTX-CrEL is safe only in the dose range of 5-10 mg/kg, and the exposure to 15-35 mg/kg caused significant weight loss (>15% and 7-9% from CrEL alone) after 2 treatments and visible signs of appetite loss, stress and pain were noted. NSP-PTX exhibited similar anti-tumor activity (inhibition of tumor growth of 181%) to PTX-CrEL (244%) in a breast cancer xenograft model at an equivalent dose (15 mg/kg) and schedule (Figure 2). PK studies revealed that PTX-NSP in murine plasma have a larger volume of distribution, higher clearance, and longer half-life than PTX-CrEL.

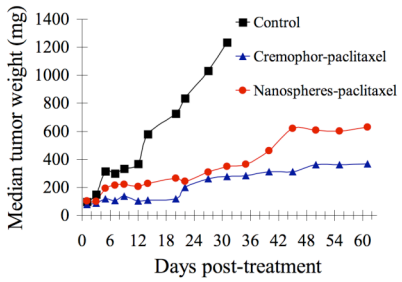

Figure 2. Anti-tumor activity in NCR nu/nu mice.

Conclusions: In vivo performance of paclitaxel-loaded tyrosine-derived nanospheres in breast cancer xenografts model is comparable to clinically used Taxol® without the toxicity exhibited by Cremophor. The evaluation of relative efficacy and potential synergies of nanospheres containing both paclitaxel and other chemotherapeutic and chemopreventative drugs such as analogues of vitamin D3 is currently under investigation.

References:

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