Enhanced tumor toxicity and reduced off-target toxicity by pretargeting mammary carcinoma with bispecific antibody complexes and dual polymer-pro- drug conjugates

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Statement of the Problem: Conventional chemotherapy is associate with severe off target toxicities. Pretargeting of high specific activity Polymer-Pro-Drug Conjugates (PPDCs) should reduce off-target toxicity and increase therapeutic efficacy. We now report enhanced therapeutic efficacy in a murine mammary carcinoma model pretargeted with Bispecific Botinylated anti-DTPA Antibody Complexes (BSAbC) and targeting with single or double PPDCs containing Doxorubicin (Dox) or Paclitaxel (Ptxl). No hematological- nor cardio-toxicity were seen in animals treated with PPDCs.

Methods: Biotin-anti-DTPA antibody BSAbC was used to pretarget murine mammary carcinoma 4T1, that over-express biotin receptors grown in Balb/C mice. Experiment treatments were as follows: placebo, Dox, Ptxl, pretargeting with BSAbC followed by DOX-PPDCs, Ptxl-PPDCs, or combination of both PPDCs injected weekly. Tumor volumes were measured daily. Then, tumors were harvested, weighed and TUNEL staining was performed to assess apoptosis. Blood samples were obtained for H &E staining to determine hematological toxicities. Hearts from experimental animals were analyzed by fluorescence microscopy for Dox cardiotoxicity.

Results: Maximal tumor growth suppression was observed in the combination PPDC treatment group (67mg). Individual DOX-PPDCs or Ptxl-PPDCs treatment were better than Dox or Ptxl treated tumors. The placebo group tumor size was 670 mg. The extent of apoptosis by TUNEL staining was inversely proportional to with tumor size. Fluorescence microscopy showed that Dox treatment had Dox fluorescence in the myocardium whereas hearts from pretargeted PPDC groups showed no Dox accumulation. There was no hematological toxicity in single PPDC or dual PPDC therapy groups whereas Dox and Ptxl treatment groups showed toxicities ($p<0.05$-0.01 respectively).

Conclusion: Biotin receptor expressing murine 4T1 carcinoma could be pretargeted and targeted with single or dual PPDCs to obtain optimal tumor regression. Both cardiotoxicity and hematological toxicities were not observed following treatment with PPDCs. This therapeutic approach could provide highly effective cancer therapy with no off-targeted toxicity.