Receptor-Mediated Chemotherapy Using a New Docetaxel-Peptide Conjugate for Sortilin-Positive Triple-Negative Breast Cancer

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Abstract

Background: Triple-negative breast cancer (TNBC) is a heterogeneous disease with still-limited defined molecular characteristics. In the last decade, targeting of specific protein expression evolution markers of tumors has emerged amongst the optimal anti-cancer strategies. Recent, increased expression of the sortilin (SORT) receptor has been reported in TNBC patients. Given SORT1 expression in protein internalization, sorting and trafficking, we developed a novel peptide-anticancer drug conjugation platform to target SORT1-positive cancer cells by linking docetaxel to a peptide (TH1902) that specifically binds SORT1. Here we are reporting the results obtained with TH1902.

Methods: We studied TH1902 conjugation, TH1902-binding properties of Sortilin-expressing cell lines, and TH1902-mediated uptake of docetaxel in breast cancer cells. The in vivo preclinical study was performed in a murine TNBC xenograft model with TH1902 and docetaxel, alone or combined.

Results: PHA-conjugation with docetaxel for Sortilin target was assessed by TH1902-internalization and enhanced apoptotic activity. In TH1902-treated tumors, significantly more apoptotic cells were observed for TH1902 than for docetaxel. In vivo, TH1902-mediated greater tumor regression was observed than in control mice. In mice treated with TH1902, we found less neutrophil infiltration and enhanced survival than in docetaxel-treated mice. In contrast, 1 treatment with unconjugated Docetaxel strongly reduced neutrophil counts.

Conclusions: This novel therapeutic platform demonstrates advantages of docetaxel delivery by targeting Sortilin-expressing cancer cells. It offers improved tolerability (lower toxicity) and improved efficacies without compromising drug concentrations. This new platform can provide a novel therapeutic tool for breast cancer treatment.