IT-141, a stabilized polymer micelle formulation, prolongs the pharmacodynamic effect of SN-38

ABSTRACT
IT-141 is a formulation of SN-38 encapsulated in an iron-stabilized polymer micelle. SN-38 is the active metabolite of irinotecan (CPT-11) which in combination with 5-FU and leucovorin is first-line FDA approved therapy for metastatic colorectal cancer. Although SN-38 is 1,000 times more potent than irinotecan alone, there is about 100-fold lower concentration of SN-38 in plasma from irinotecan. In the clinic only 2% to 10% of the administered dose of irinotecan is converted by carboxylesterase to SN-38 and there is great interpatient variability with toxicity. In vitro, IT-141 demonstrated nanomolar IC50s against a panel of human cancer cell lines in comparison to irinotecan’s micromolar IC50 concentrations. SN-38 binds to the topoisomerase I DNA complex resulting in double stranded breaks and cell death. We compared the mechanism of action of IT-141 compared to irinotecan treatment in HT-29 xenografts. We demonstrated the incidence of double stranded breaks by immunohistochemistry (IHC) of γ-H2AX expression in tumors treated with IT-141 compared to irinotecan treatment at different time points (24, 48, 72 and 144 hours). In irinotecan treated tumors, γ-H2AX expression peaked at 72 hours followed by a sharp decrease in expression at 144 hours. In IT-141 treated tumors, γ-H2AX positive staining increased steadily from 24 through 144 hours. This shift in the kinetics of the mechanism corroborates the biodistribution studies where IT-141 delivered 28-fold more SN-38 to the tumor compared to irinotecan. The AUC and Cmax of IT-141 treated tumors was 30.9 mg·h/kg and 12.2 mg·h respectively compared to an AUC of 1.1 mg·h/kg and a Cmax of 0.2 mg/kg in the Irinotecan treated tumors. In an HT-29 xenograft model, IT-141 inhibited tumor growth by 157% compared to 57% with irinotecan. IT-141 demonstrates successful encapsulation of SN-38 leading to a safer, more effective formulation. Our DNA damage assay demonstrated that IT-141 extended the pharmacodynamic effect over irinotecan in treated tumors. Further studies are required to determine the duration of IT-141’s pharmacodynamics effect. This data validates the increased tumor accumulation of SN-38 and increased efficacy of IT-141 over irinotecan.

RESULTS
IT-141 demonstrates comparable IC50 to SN-38 free drug and significantly improved IC50 over irinotecan in vitro

PHOTOGRAPHS

CONCLUSIONS
IT-141 increases biodistribution of SN-38 and improves anti-tumor efficacy over irinotecan

Biodistribution profile of SN-38 in HT-29 tumor-bearing mice demonstrated SN-38 was 28-fold higher in tumor from IT-141 over SN-38 from irinotecan.

Immuno-histochemical analysis for the presence of DNA double stranded breaks using γ-H2AX in HT-29 xenograft tissues treated with IT-141 or irinotecan for 24h, 48h, 72h, and 144h. IT-141 and irinotecan demonstrated increased expression of γ-H2AX in a time dependent fashion, but IT-141 treated tumors consistently showed significant increase in γ-H2AX expression levels through 144h.

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