Poster: 639

DDS-06E - A novel oral pH-sensitive micellar formulation of SN38: Effect of dosing regimen on efficacy and tolerability using a human colon xenograft model.

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Introduction

Irinotecan (CPT-11) is among the most widely used chemotherapeutic agents for metastatic colorectal cancer but treatment emergent adverse events, such as early- and late-stage diarrhea, significantly impact patient quality of life and preclude use in the adjuvant setting. Preclinical and clinical studies have shown SN38, the active metabolite of CPT-11, to provides effective antitumor activity while reducing the risk of serious adverse events associated with CPT-11. We are developing an oral micellar formulation of SN38 (DDS-06E) using novel amphiphilic, pH sensitive, diblock copolymers of polyethyleneglycol-polymethacrylate (PEG-PMA) to deliver the drug to the upper GI. In these studies, we evaluated the efficacy and tolerability of this new oral formulation in murine human colorectal tumor xenografts under 2 dosing regimen.

Objective

- To evaluate the tolerability and efficacy of DDS-06E when administered orally to SWISS nude mice bearing human colon HCT-116 tumor xenografts using 2 distinct dosing regimen.

Materials and Methods

Preparation of DDS-06E formulations: DDS-06E formulations were prepared at a drug loading level of 10% wt/wt (SN38:PEG-PMA). Aqueous solutions of PEG-PMA and alkaline SN38 were mixed, neutralized and lyophilized. Vials were reconstituted with phosphate buffer (PBS) (pH 6.8) for administration to animals. Dosing solution analyses were performed using HPLC (Waters).

In vivo antitumor activity: HCT-116 human colon tumor cells were subcutaneously implanted to SWISS nude mice. Tumors were allowed to grow to 80-100 mm^3 prior to starting treatment. For regimen 1, two groups of mice (n=24) received DDS-06E at 25 or 75 mg/kg (Q1Dx13), by oral gavage, one group received CPT-11 (n=10; Q7Dx2) intravenously and one group received vehicle only (n=10) again by oral gavage (Q1Dx13). For regimen 2, groups of mice (n=12) received either DDS-06E by oral gavage at doses of 12.5 to 75 mg/kg [(Q1Dx5)x2] every 21 days), CPT-11 intravenously (n=10; Q7Dx2 every 21 days) or vehicle by oral gavage (n=10; [(Q1Dx5)x2] every 21 days). Body weights, tumor volumes ((width^2 x lenght)/2), signs of toxicity (diarrhea), and survival were recorded. All in vivo experiments were performed in compliance with ethical guidelines.

Release Mechanism of DDS-06E

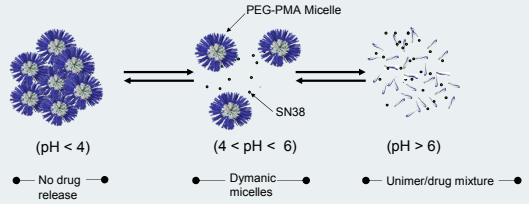

Figure 1: Release mechanism of DDS-06E micellar formulation.. The range of particle size of DDS-06E upon reconstitution is typically between 150 to 300 nm.

In vivo efficacy

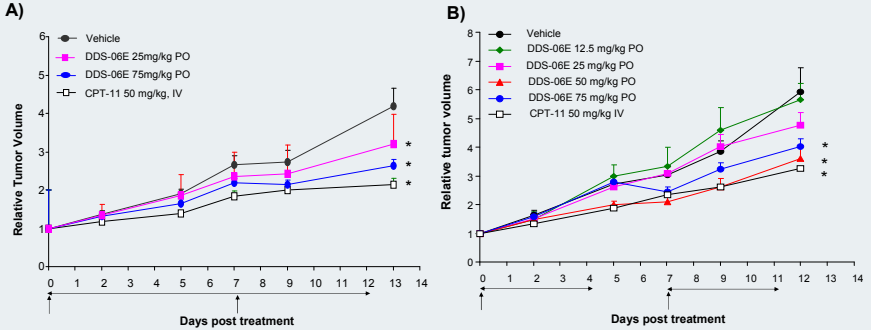

Figure 2: Efficacy of DDS-06E after oral administration to SWISS nude mice bearing human HCT-116 colorectal carcinoma xenografts **(A)** Regimen 1: Animals received either vehicle (PBS; n = 10), DDS-06E at 25 mg/kg and 75 mg/kg PO (n = 24) or CPT-11 50 mg/kg IV (n = 10). DDS-06E and vehicle were administered once a day by oral gavage (PO) for 13 consecutive days; CPT-11 was given IV on days 0 and 7. **(B)** Regimen 2: DDS-06E was administered by oral gavage for 5 consecutives days for 2 weeks; CPT-11 was given IV on days 0,7 (n = 12) Results are presented as relative tumor volume ± SEM. Horizontal arrows represent DDS-06E treatment periods and vertical arrows represent CPT-11 treatment days. * p < 0.05 compared to vehicle control.

Table 1: Treatment effects of oral DDS-06E, IV CPT-11 and Vehicle on HCT-116 tumor xenografts in SWISS nude mice. Dosing as Figure 2. * p < 0.05 compared to vehicle control. † p > 0.5 compared to CPT-11

Regimen 1	Mean Relative Tumor Volume ± SEM (on Day 13)	T/C% (on D13, end of treatment cycle)	Mean Doubling Time ± SD (days)
Vehicle	4.2 ± 0.5	---	6.4 ± 1.6
CPT-11 50 mg/kg	2.1 ± 0.2 *	68	11.1 ± 2.5
DDS-06E 25 mg/kg	3.2 ± 0.8 *	82	8.3 ± 2.2
DDS-06E 75 mg/kg	2.6 ± 0.2 *†	69	9.3 ± 3.9
Regimen 2	**Mean Relative Tumor Volume ± SEM (on Day 12)**	**T/C% (on D12)**	**Mean Doubling Time ± SD (days)**
Vehicle	5.9 ± 0.8	---	5.6 ± 1.0
CPT-11 50 mg/kg	3.3 ± 0.4 *	55	7.9 ± 1.3 *
DDS-06E 12.5 mg/kg	5.7 ± 0.6	88	6.2 ± 1.0
DDS-06E 25 mg/kg	4.8 ± 0.4	83	6.9 ± 1.8*
DDS-06E 50 mg/kg	3.6 ± 0.4 * †	57	7.7 ± 1.6 * †
DDS-06E 75 mg/kg	4.0 ± 0.3 * †	71	7.9 ± 1.3 * †

Tolerability in nude mice

Table 2: Nude mice received single or multiple daily administrations of DDS-06E. Mice were monitored for mortality and signs of toxicity. Mice were sacrificed if body weight loss was > 15% for three consecutive days or > 20% for one day.

Compounds	Route	Doses (mg/kg)	Maximal Body Weight Loss (Day post treatment initiation)
DDS-06E Repeated dose Q1Dx13	PO	25 75	11.7% (D13) 10.7% (D13)
CPT-11 (Q7D)x2	IV	50	6.3% (D7)
DDS-06E Repeated Dose (Q1Dx5)x2	PO	12.5 25 50 75	1.3% (D12) 1.8% (D12) 1.4% (D12) 1.5%(D12)
CPT-11 (Q7D)x2	IV	50	4.0%(D12)

Discussion and Conclusions

The efficacy and tolerability of DDS-06E, a pH-sensitive micellar formulation of SN38 for oral dosing, were evaluated in human HCT-116 colorectal tumor xenograft using two different prolonged dosing regimens. The following observations were made during the studies;

- These data suggest that DDS-06E promotes the oral bioavailibility of SN38 and that SN38 delivered in this way may access tumor sites effectively.

- In both studies, DDS-06E administered orally at 50 and/or 75 mg/kg doses demonstrated tumor growth reductions equivalent (P > 0.05) to weekly intravenous injections of CPT-11. Animals receiving CPT-11 showed signs of shock following each injection and 19% of them died post injection.

- DDS-06E was well tolerated in these studies; there were no overt signs of toxicity (body weight loss, diarrhea) after two weeks of treatment. Less than 10% of animals under regimen 1 and no animals under regimen 2 died or where sacrificed.

While DDS-06E under regimen 2 showed evidence of greater tolerability, efficacy was comparable between the two regimen. Comparable efficacy and favorable tolerability was demonstrated in both studies when compared to intravenous CPT-11. Regimen 2 is therefore favored for further studies.