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Article Tools

DEVELOPMENTAL THERAPEUTICS: CYTOTOXIC CHEMOTHERAPY

Phase I study of liposome encapsulated irinotecan (PEP02) in advanced solid tumor patients

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Abstract

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Background: PEP02 is a novel nanoparticle liposome formulation of irinotecan aiming to enhance tumor localization and improve pharmacokinetic properties of irinotecan and its active metabolite-SN38. The aims of the study are to define the dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and pharmacokinetics (PK) of PEP02 in patients with advanced refractory solid tumors. **Methods:** Pts with advanced refractory solid tumors, ECOG PS 0–1, and adequate hematological, hepatic and renal functions were eligible. PEP02 was given as 90mins i.v. infusion, repeated every 3 weeks. The doses would have been escalated from 60, 120, 180 to 240 mg/m^2 in a single-patient cohort accelerated titration design. PK samples were collected on days 1, 2, 3, 8 and 21. **Results:** A total of 11 pts (M/F 1/10; median age 47, range 41–67) were enrolled onto three dose levels, with 1, 6 and 4 pts at dose level I (60 mg/m^2), II (120 mg/m^2) and III (180 mg/m^2), respectively. DLT was observed in 3 pts, including 1 at dose level II (grade 3 catheter-related infection) and 2 at dose level III (grade 3 diarrhea and febrile neutropenia in 1 and treatment-related mortality secondary to grade 4 diarrhea and neutropenia in 1). MTD was determined as 120 mg/m^2. The PK of total irinotecan after PEP02 dosing were characterized by, i.e. after 120 mg/m^2, low clearance (mean = 0.0591 L/m^2/hr), small volume of distribution (mean = 1.8 L/m^2, similar to plasma volume), and prolonged terminal half-life (mean=29.5 hr). The plasma concentration-time profiles of encapsulated irinotecan (PEP02) in each pt matched approximately with those of total irinotecan indicating that the release of irinotecan from liposomes occurred slowly over time. Comparing with published PK parameters after 125 mg/m^2 of irinotecan, the Cmax of

SN-38 after 120 mg/m2 of PEP02 was lower (9.2±3.5 vs 26.3±11.9 ng/mL), the terminal t1/2 of SN-38 was longer (75.4±43.8 vs 10.4±3.1 hrs) and the AUC of SN-38 was larger (710±395 vs 229±108 ng.h/mL). The best response of 10 evaluable pts was PR in 2 (cervical and pancreatic cancer) and SD in 3. **Conclusions:** The MTD of PEP02 monotherapy at 3-week interval is 120 mg/m^2, which will be the recommended dose for future phase II studies. Preliminary data suggest that PEP02 exhibits encouraging pharmacokinetic, safety and efficacy profiles.

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