A Phase 1 Study of the Oral Administration of Irinotecan in Combination With the Potent P-glycoprotein (P-gp) Inhibitor Encequidar (NCT02250157)

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INTRODUCTION

Irinotecan is a prodrug of the potent topoisomerase inhibitor SN-38. The potential advantages of oral irinotecan administration include prolonged blood levels, less toxicity, greater convenience, reduced cost, and possible increased patient adherence compared to IV administration. Adhesive intraperitoneal-filling capsule formulations of P-glycoprotein (P-gp)-active transport substrates such as irinotecan and irinotecan derivatives slow the gastrointestinal transit and prevent systemic absorption and intraluminal accumulation of various cytotoxic agents. Many chemotherapy agents are substrates for P-gp and have poor oral bioavailability and active efflux from the intestinal epithelium. The administration of irinotecan, a highly specific and potent blocker of P-gp, allows for absorption of chemotherapeutic agents across the intestinal epithelium and into the systemic circulation. Encequidar, selectively binds to and inhibits P-gp, leading to an increase in both oral bioavailability and therapeutic efficacy.

OBJECTIVES

- The primary objective of this study was to determine the maximum tolerated dose and dose-limiting toxicity of orally administered irinotecan and encequidar encequidar once daily for 7 days in combination.
- Secondary objectives were to determine the recommended phase 2 dose and the pharmacokinetics of orally administered irinotecan.
- Pharmacokinetics of encequidar.

METHODS

- Thirty male and female patients, mean age 60.9 years (range 33-78) were enrolled into this ongoing study. Patients were administered, under fasting condition, encequidar 15 mg and oral irinotecan 20, 40, 80, 120, 160, 200, 240 mg/m2 dose levels on day 1 of a 21-day cycle.

RESULTS

- The most common cancers were ovarian (6), colorectal (4), breast (4), endometrial (3), and pancreatic (3) and patients had a median Karnofsky performance status of 0-1, and were not homozygous for UGT 1A1*28.
- Thirty (30) patients were evaluable for toxicity.
- The most common grade 1-2 adverse events were nausea (67%), diarrhea (53%), vomiting (43%), abdominal pain (43%), and constipation (33%).
- The most common grade 3-4 adverse events were nausea (20%), abdominal pain (20%), vomiting (13%), and diarrhea (13%).
- Treatment-related serious adverse events were experienced by 6 (20%) patients (nausea or vomiting).
- Acute cholinergic diarrhea has not been observed.

CONCLUSIONS

- Oral administration of encequidar followed by irinotecan tablets results in pharmacologically active concentrations of SN-38.
- Confirmation of the maximum tolerated dose when dosed on a 21-day cycle is ongoing.
- Phase 2 studies are being planned.