Irinotecan and UFT/Leucovorin in Patients With Advanced Cancers

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The combination of irinotecan and fluorouracil (5-FU) is synergistic when applied to human colon cancer cell lines in vitro and appears to be schedule-dependent: maximal activity occurs when irinotecan is administered prior to 5-FU. In this phase I study, irinotecan is administered in combination with UFT and leucovorin in patients with advanced solid tumors.

Introduction

The combination of irinotecan (CPT-11, Camptosar) and fluorouracil (5-FU) has proven to be an effective agent against advanced malignancies. Furthermore, maximal activity occurs when irinotecan is administered prior to 5-FU [1,2]. Recent randomized trials have shown the combination to produce improved response rates, progression-free survival, and overall survival when compared to 5-FU alone in patients with metastatic colorectal cancer [3,4].

This phase I trial is an evaluation of sequential, ascending doses of irinotecan combined with UFT (uracil and tegafur) plus oral leucovorin (a combination being developed under the trade name Orzel) in a fixed dose when administered to patients with advanced malignancies.

Objectives

This trial is designed to (1) determine the maximum tolerated doses of combined irinotecan and UFT plus leucovorin at 60 mg/d when administered to patients with cancer; (2) describe the toxicities observed with the combination; (3) describe the pharmacokinetics of each drug when administered in this combination; and 4) obtain preliminary evidence of antitumor activity.

Eligibility Criteria

Patients with histologically confirmed solid tumors, measurable or evaluable disease, and no effective treatment options are eligible. Other requirements are Eastern Cooperative Oncology Group performance status of 0 to 2 and no chemotherapy/radiotherapy for 3 weeks prior to study entry. Baseline laboratory values are absolute granulocyte count \( \geq 1,500 \times 10^9/L \); platelet count \( \geq 100,000 \times 10^9/L \); serum creatinine \( \leq 2.0 \text{ mg/dL} \); total bilirubin \( \leq 1.5 \text{ mg/dL} \); aspartate aminotransferase/alanine aminotransferase \( \leq 2.5 \times \text{ upper limit of normal} \).

Patient characteristics are shown in Table 1.

Treatment Schedule

Treatment consists of escalating doses of irinotecan as a 90-minute intravenous infusion on day 1, followed by oral UFT twice daily on days 2 through 15, and a fixed dose of oral leucovorin twice daily on days 2 through 15. Starting doses were irinotecan 200 mg/m²/d, UFT 200 mg/m²/d, and leucovorin 60 mg/d. Cycles are repeated every 21 days (Table 2).

Toxicity

Dose-limiting toxicity is defined as grade 4 neutropenia lasting > 5 days, grade 3/4 neutropenia with fever > 101°F, platelet count < 25,000 \( \times 10^9/L \), and grade 3/4 nonhematologic toxicity. Maximum tolerated dose is defined as one dose level below the doses that produced dose-limiting toxicity in more than one third of patients. A total of 10 to 12 patients will be treated at the maximum tolerated dose to better define these as the recommended doses for phase II evaluation.

One patient with non-small-cell lung cancer (NSCLC) treated at the initial dose level experienced
dose-limiting toxicity in the form of grade 4 diarrhea, nausea/vomiting, and mucositis, prompting expansion of that level to six patients. Of the patients evaluable for antitumor response, the patient noted above maintained stable disease following two cycles of therapy and continues on treatment. Irinotecan, SN-38, and 5-FU pharmacokinetic analyses will be performed on all patients. (Irinotecan is a soluble prodrug that is converted in vivo to the highly active SN-38.) Accrual continues at the initial dose level. (Toxicity results are outlined in Table 3.)

**Efficacy**

Only three patients are evaluable for response to date. One patient with NSCLC chose to discontinue treatment after one cycle, and one patient has yet to complete cycle 2. One patient has stable disease and two have experienced disease progression.

Another patient with NSCLC who received prior docetaxel (Taxotere), vinorelbine (Navelbine), and gemcitabine (Gemzar) maintained disease stabilization at her metastatic sites after two cycles and continues on therapy. Two patients with colon cancer experienced disease progression after one and two treatment cycles, respectively.

**Conclusions**

Preliminary results indicate that the combination of irinotecan and UFT plus leucovorin is well tolerated at these initial doses, although dose-limiting toxicity was observed in one patient. Antitumor activity was observed in one patient with NSCLC. Accrual continues at the initial dose level (expanded to six patients), and pharmacokinetic analyses are ongoing.

**References:**


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