UFT Plus Calcium Folate/Irinotecan in Colorectal Cancer

This phase I trial combining UFT plus oral calcium folinate (Orzel) with irinotecan (CPT-11) (Camptosar) for the treatment of patients with advanced or metastatic colorectal cancer.

Introduction

The single most important agent for the systemic management of colorectal cancer remains 5-fluorouracil (5-FU), both as adjuvant treatment and in advanced disease. Over the last 40 years, a wide range of 5-FU schedules have been used, and in parts of the world, it is now generally accepted that 5-FU is most effective when given over a prolonged period with modulation by calcium folinate. In the United States, the preferred schedule is prolonged 5-FU infusion plus calcium folinate (leucovorin). One of the limitations of 5-FU is that oral administration is not feasible. However, prolonged infusion has important practical implications, such as the need for hospital admission or placement of a long-term central venous catheter. In addition, 5-FU has significant toxicities due to its lack of specificity. UFT(uracil plus tegafur in a 4:1 molar ratio) plus oral calcium folinate (Orzel) is a novel, oral fluoropyrimidine compound developed with the aim of offering more convenient and better-tolerated therapy.

Initial Phase I and II Trials

Uracil and the fluoropyrimidine tegafur are combined in a molar ratio of 4:1. Tegafur is converted to 5-FU in vivo; uracil is a pyrimidine that inhibits the enzyme dihydropyrimidine dehydrogenase, which controls the rate-limiting step in the degradation of 5-FU to 2-fluoro-β-alanine. Fujii et al.[1] have shown that the combination of uracil with tegafur increases the accumulation of 5-FU in tumors and enhances its antitumor activity in xenograft models without increased toxicity.

Given as a single agent, UFT plus oral calcium folinate has been evaluated in a wide range of clinical trials. Initial phase I and II trials were carried out in Japan,[2] and in the United States, phase I studies with UFT plus oral calcium folinate used single weekly, 5-day, and 28-day dosing schedules. These studies identified phase II doses for each schedule. Phase I studies using different UFT dose schedules in combination with a fixed dose of calcium folinate were extended in phase II trials to combine fixed-dose UFT with high-dose (150 mg) or low-dose (15 mg) calcium folinate. Again, the activity of UFT plus oral calcium folinate was confirmed,[3] leading to two large multicenter phase III trials comparing UFT plus oral calcium folinate with conventional 5-FU-based treatment.

Irinotecan

Irinotecan (CPT-11) (Camptosar) is a semisynthetic derivative of camptothecin, a plant alkaloid derived from the tree Camptotheca acuminata. Irinotecan is converted to the active metabolite SN38, which inhibits the enzyme DNA topoisomerase I, leading to lethal, single-strand DNA breaks.[4] In preclinical studies, irinotecan was active against a range of tumor types,[5] including those expressing P-glycoprotein.[6] Phase I clinical studies were carried out in Europe and Japan. In European studies, the dose-limiting toxicities were neutropenia and diarrhea.[7-9] Based on results from these trials, a dose of 350 mg/m² given as an intravenous infusion over 60 to 90 minutes every 3 weeks was selected for European phase II trials. By contrast, studies in Japan and in the United States are utilizing irinotecan doses of 125 mg/m² or 150 mg/m² given weekly or biweekly. Irinotecan is commercially available as second-line treatment for patients with metastatic colorectal cancer,[10] and has been shown to be superior to best supportive care or retreatment with 5-FU in this setting. Irinotecan has been given in combination with 5-FU in phase I studies carried out in Japan, the United States, and Europe. A range of doses and schedules of both compounds has been evaluated. In a United States study, the maximum tolerated dose for 5-FU was 500 mg/m² and 120 mg/m² for irinotecan when given weekly.[11] This suggests that, although there are overlapping toxicities with these two agents, they can be administered together, with irinotecan given at the full single-agent dose. Although preliminary studies in Japan raised the possibility of a pharmacokinetic interaction.
between 5-FU and irinotecan,[12] this has not been confirmed in subsequent trials.[13]

**Rationale for Current Study**

5-Fluorouracil remains the single most widely used agent for the treatment of advanced colorectal cancer. Irinotecan was the first agent shown to be active in 5-FU-resistant disease. Since irinotecan and 5-FU have different mechanisms of action and appear to be non-cross-resistant in the clinic, it is important to look at combinations of irinotecan and fluoropyrimidines. A combination of the 5-FU prodrug UFT plus oral calcium folinate has activity similar to that of 5-FU in advanced colorectal cancer, but potential benefits in terms of its mode of administration and toxicity profile. The combination of irinotecan and UFT plus oral calcium folinate offers the prospect of a highly active regimen that is convenient for the patient and easily administered. It is likely that combination therapy will be of most value as first-line treatment for advanced colorectal cancer, and it is for this group of patients that larger, randomized studies are envisaged. The current dose-finding phase I study of UFT plus oral calcium folinate and irinotecan has been restricted to this group of patients in order that the study results are applicable to future trials.

The aims of the study are 1) to determine the maximum tolerated dose of UFT plus oral calcium folinate and irinotecan and to identify a dose of the combination for future trials, and 2) to determine the side-effect profile and the response rate of patients with advanced metastatic or colorectal cancer treated with UFT plus oral calcium folinate and irinotecan.

**Trial Design**

This is a nonrandomized, open-label, two-center phase I trial designed primarily to determine the safety and maximum tolerated dose of UFT plus oral calcium folinate and irinotecan given in escalating doses with a fixed dose of calcium folinate. Initially, six patients will be treated with irinotecan 200 mg/m² given as a 90-minute IV infusion on day 1, and UFT 250 mg/m²/d with calcium folinate 90 mg/d, both given orally in three divided doses over 14 days. This will be followed by a 1-week rest period; treatment will recommence if the patient does not experience dose-limiting toxicities or progressive disease, and wants to continue treatment (Figure 1). Dose escalation will continue in subsequent cohorts as shown in Table 1. In brief, with the calcium folinate dose fixed at 90 mg/d, the dose of irinotecan will be increased from 200 to 250 mg/m², then to 300 mg/m². If this is tolerated, the dose of UFT will be escalated from 250 to 300 mg/m²/d, then to 350 mg/m²/d. The maximum tolerated dose will be the dose at which more than two of six patients experience dose-limiting toxicities during the first cycle of treatment. Dose-limiting toxicities include grade 3 or 4 neutropenia complicated by fever, requiring IV antibiotics, associated with grade 3 or 4 diarrhea, or persisting for more than 7 days. Grade 4 thrombocytopenia and grade 3 or 4 nonhematologic toxicities, with the exception of alopecia or nausea and vomiting, will also be dose-limiting.

Disease sites will be assessed at baseline and after every three cycles of treatment while on study and at the end of treatment. In most cases, assessment will be by computed tomography scan with additional imaging performed where clinically indicated.

**Eligibility**

Eligible patients will have histologically or cytologically confirmed colorectal cancer that is either advanced or metastatic. They must have measurable disease and be aged 18 years or older. Patients who have received prior adjuvant chemotherapy performed more than 6 months prior to study entry are eligible. (Patients who have received prior chemotherapy for advanced disease and those who completed adjuvant treatment less than 6 months prior to possible study entry are ineligible.) Patients must have Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 with adequate hematologic and biochemical reserve, and all patients must give informed consent to be eligible for study entry. Patients who are known to have brain metastases, bowel obstruction, or any condition that may affect absorption of UFT plus oral calcium folinate will be excluded. Likewise, patients with other serious uncontrolled medical conditions will be excluded. The use of halogenated antiviral agents along with UFT plus oral calcium folinate or 5-FU may result in severe myelosuppression or central nervous system toxicity, and thus the use of these drugs is contraindicated.

**Dose Modification**

On day 1 of each cycle, chemotherapy will only start provided the blood count has recovered satisfactorily and other toxicities such as diarrhea return to baseline. If this has not occurred, treatment will be delayed until resolution.
If a patient develops significant myelosuppression or neutropenia during treatment, UFT plus oral calcium folinate will be withheld until this resolves. Similarly, if other significant toxicities such as diarrhea develop, treatment will be discontinued until they improve. Growth factor may be given where clinically indicated in patients with complicated neutropenia. Delayed diarrhea will initially be treated with loperamide, and the patient will be hospitalized if the diarrhea persists at 48 hours, as would be standard practice with irinotecan. Where it is appropriate for a patient to continue UFT plus oral calcium folinate and irinotecan following an episode of significant toxicity, dose modification will be made for subsequent treatment cycles.

Response Assessment

Although efficacy is not a standard end point within conventional phase I studies, it will be assessed in the current trial. This is appropriate because the patients being treated will be receiving agents with known activity against colorectal cancer when administered alone, they will not have received prior chemotherapy for advanced disease, and they will have measurable lesions on study entry. Therefore, a meaningful assessment of antitumor activity can be made, especially in the expanded cohort of patients treated at the proposed phase II dose.

Conclusions

After 40 years during which 5-FU was effectively the sole agent with proven activity in colorectal cancer, there are now exciting prospects for new developments for the treatment of this common malignancy. UFT plus oral calcium folinate is one of a group of oral fluoropyrimidines that offer potentially significant advantages over standard 5-FU treatment. Other agents such as irinotecan and oxaliplatin have proven activity against colorectal cancer and act by mechanisms quite distinct to those of 5-FU. It is important now to define parameters for the optimal combination of new fluoropyrimidines such as UFT plus oral calcium folinate and other novel cytotoxic agents such as irinotecan. The current study will identify the pattern of toxicities, and should confirm the activity of UFT plus oral calcium folinate and irinotecan. It will enable a large, randomized phase III trial to be undertaken comparing the combination with standard 5-FU-based treatment in patients with advanced or metastatic colorectal cancer.

References:


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