UFT/Leucovorin Plus Weekly Irinotecan in Advanced or Metastatic Colorectal Cancer

Review Article [1] | October 01, 2000
By Georgia Schilling, MD [2], Rainer Lipp, MD [3], Susanna Hegewisch-becker, MD, PhD [4], and Dieter Kurt Hossfeld, MD, PhD [5]

This is an open-label, nonrandomized phase I trial to determine the safety and maximum tolerated dose of irinotecan with a fixed dose of UFT plus oral leucovorin in patients with advanced or metastatic colorectal cancer.

Introduction

The combination of irinotecan (Camptosar, CPT-11), a topoisomerase I inhibitor, with fluorouracil (5-FU) has been used successfully to treat advanced colorectal cancer. In large clinical trials there were significant advantages for this combination compared with 5-FU/leucovorin alone. The main toxicities and dose-limiting toxicities (DLTs) of this combination were diarrhea, nausea, and neutropenia.

UFT (uracil and tegafur) has shown efficacy in advanced colorectal cancer both as a single agent[1,2] and in combination with oral leucovorin (a combination being developed under the trade name Orzel).[3-5] UFT possesses significant benefits over 5-FU in terms of its route of administration, toxicity profile, and pharmacokinetics. Furthermore, UFT is well tolerated, is less myelosuppressive than 5-FU (< 5% for UFT compared with up to 20% for 5-FU), and results in a lower incidence of nausea and vomiting.[6-10]

Because of the oral administration of UFT plus leucovorin, there may be additional advantages for its combination with irinotecan.

The primary objectives of the study are the determination of the maximum tolerated dose (MTD) of the combination of irinotecan with a fixed dose of UFT plus oral leucovorin; establishment of the starting dose for the phase II study; determination of the side-effect profile; and assessment of the DLT of the combination of irinotecan and UFT plus leucovorin. Secondary objectives are the determination of the response rate in patients with advanced or metastatic colorectal cancer and the pharmacokinetics of irinotecan.

Study Design

This phase I, open-label, dose-escalation trial is designed to determine the safety, DLTs, and MTD of irinotecan with a fixed dose of UFT plus leucovorin in patients with advanced or metastatic colorectal cancer.

One cycle of treatment will be of a 6-week duration. A maximum of six cycles of treatment will be administered per cohort, as shown in Table 1.

Initially, three of six patients will be treated weekly for 4 weeks. The combined regimen will be followed by a 2-week rest period, thus ending the cycle. At the end of the first cycle, providing DLT occurs in one or fewer of three patients, the remaining three patients of the first cohort will be treated with the same dose schedule. If two or fewer of six patients in this cohort experience a DLT, the dose level of irinotecan will be escalated for the next cohort of three to six patients; otherwise dose escalation stops. If no DLTs are observed in the first three patients of the cohort, this cohort level will close and the next three patients will begin treatment in the second cohort. This will be the case in all cohorts if no DLTs are observed in the first three patients (Figure 1).

The patients in each cohort will continue to receive the assigned dose schedule until disease progression is determined or unacceptable toxicity occurs, for a maximum of six cycles. Cohorts of three to six patients will be treated at each dose level until the MTD is reached. The MTD of irinotecan in combination with UFT plus leucovorin is defined as that dose level at which DLTs occur in more than two of six patients. Having established the MTD, the cohort below the MTD (starting...
dose for phase II) will be expanded to include 20 patients to more fully characterize the toxicity profile.

**Inclusion Criteria**

Inclusion criteria are as follows: (1) histologically confirmed advanced or metastatic colorectal carcinoma; (2) adjuvant chemotherapy (> 6 months prior to study entry); (3) no prior chemotherapy, but disease for which treatment with fluoropyrimidine or topoisomerase I inhibitors may be appropriate; (4) measurable or evaluable disease; (5) male or female (with negative pregnancy test); (6) age ≥ 18 years; (7) Eastern Cooperative Oncology Group performance status 0 to 2; (8) adequate serum chemistry; (9) adequate bone marrow function; (10) possible follow-up of the patient; and (11) patient[s] consent according to local Ethics Committee requirements.

**Exclusion Criteria**

Exclusion criteria are as follows (1) prior radiotherapy except palliative radiotherapy for control of symptomatic disease; (2) life-threatening toxicities as a result of fluoropyrimidine treatment; (3) medical or psychiatric contradiction; (4) known brain metastases; (5) ulcerative colitis or Crohn’s disease; (6) pregnant or breast-feeding women, or women not using adequate methods of birth control; (7) any condition or therapy that may pose a risk to the patient or interfere with study objectives; and (8) any other investigational drug given within 30 days of initiation of therapy, and participation in other clinical studies.

**Conclusions**

Two patients have been enrolled in the first treatment level to date. Study recruitment is ongoing. The first results will be expected in a few months.

**References:**


1999.

Source URL:
http://www.diagnosticimaging.com/review-article/uftleucovorin-plus-weekly-irinotecan-advanced-or-metastatic-colorectal-cancer

Links:
[1] http://www.diagnosticimaging.com/review-article