Oxaliplatin and UFT/Oral Calcium Folinate for Advanced Colorectal Carcinoma

By Paulo M. Hoff, MD, FACP [2] and Richard Pazdur, MD [3]

Oxaliplatin is a unique platinum compound with single-agent activity in both chemotherapy-naïve colorectal cancer patients and patients who progressed on 5-fluorouracil (5-FU). The combination of oxaliplatin and 5-FU

Introduction

Despite many advances in diagnosis and treatment of early lesions, colorectal cancer continues to be a significant problem in the United States.[1] Approximately 40% to 50% of patients diagnosed with colorectal cancer will develop metastatic disease. Currently available therapy is far from satisfactory.[2] Combination therapy with 5-fluorouracil (5-FU) and oral calcium folinate produces a response in about 25% to 30% of patients with metastatic colorectal cancer and can provide palliation and modest impact on overall survival.[3-6] The current second-line agent for treatment of patients with 5-FU-resistant colorectal cancer is irinotecan (CPT-11) (Camptosar), which provides a small, albeit statistically significant survival advantage over supportive care[7] and infusional 5-FU.[8]

Tegafur is a prodrug that is hydroxylated and converted to 5-FU by hepatic microsomal enzymes.[9] Uracil is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), which forces drug out of the catabolic pathway, leading to increased and sustained serum levels of 5-FU.[10] The addition of uracil to tegafur in a 4:1 molar concentration resulted in the clinical development of UFT.[11] Based on experience using oral calcium folinate to modulate 5-FU, research was initiated to evaluate UFT plus oral calcium folinate (Orzel). The maximum tolerated dose of this combination was found to be 300 mg/m²/day of UFT plus 150 mg/day of oral calcium folinate given in three divided doses daily for 28 days with 7 days of rest.[12,13] Phase II studies showed the regimen of UFT plus oral calcium folinate to be well tolerated, the main side effect being diarrhea.[14] Response rates varying from 25% to 42% were observed.[14,15]

Hand-foot syndrome is a side effect with protracted intravenous infusions of 5-FU or capecitabine (Xeloda), but it has not been observed with UFT plus oral calcium folinate. In addition, when UFT plus oral calcium folinate is administered in a 28-day schedule, grades 3 and 4 neutropenia and stomatitis are markedly less than with 5-FU plus oral calcium folinate, which is associated with these toxicities in over 40% of treated patients.

Single-agent oxaliplatin has shown a response rate of approximately 10% in patients whose disease progressed on a 5-FU-based regimen.[16] Adding oxaliplatin to 5-FU regimens in previously treated patients produces responses in 25% to 30% of patients.[17] In previously untreated patients, response rates as high as 40% to 60% with median survival in excess of 15 months have been reported.[18,19] The above results of the oxaliplatin/5-FU-based regimens provide the rationale for combining oxaliplatin and UFT plus oral calcium folinate. This regimen may produce similarly good results with an improved toxicity profile. This phase I study has been designed to determine the dose of oxaliplatin combined with UFT plus oral calcium folinate suitable for future phase II studies of this combination in metastatic colorectal cancer patients.

Patients and Methods

An estimated 30 patients with advanced colorectal adenocarcinoma will be entered onto this single-site, open-label, phase I study of oxaliplatin administered intravenously once every 2 weeks in combination with UFT plus oral calcium folinate given for 3 weeks (21 days, as 5 days of drug administration followed by 2 days of rest; cycles are repeated every 28 days). Antitumor response will be documented but the determination of response rate is not a study objective.
The regimen of drug administration will be based on a 4-week schedule to maintain the established schedule and starting dose of oxaliplatin (85 mg/m² every 2 weeks). The schedule of UFT plus oral calcium folinate therefore will be adapted from a 35-day cycle (drugs given on days 1 through 28) to a 28-day cycle (drugs given for 5 days followed by 2 days of rest from days 1 through 21, for a total of three courses in each cycle). The 2-day rest period was added in an attempt to decrease gastrointestinal toxicity.

To participate in this study patients must have histologically proven advanced/metastatic colorectal cancer; have received prior chemotherapy with both 5-FU and irinotecan; have measurable or evaluable disease; and give informed consent acknowledging that they have been informed of the experimental nature of the trial. Patients must be ≥ 18 years of age; have an Eastern Cooperative Oncology Group performance status of 0 or 1; have adequate bone marrow, liver, and renal functions; have not received prior chemotherapy or radiotherapy within the last 4 weeks (≥ 6 weeks if mitomycin or a nitrosourea); and have completely recovered from treatment-related toxicities. Patients who are sterile must agree to use medically effective contraception throughout the treatment.

Patients are ineligible for the study if they have received prior treatment with oxaliplatin; have any active or uncontrolled infection, including known infection with the human immunodeficiency virus; have a history of myocardial infarction within the previous 6 months or current clinical evidence of congestive heart failure; have history of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix) in the last 5 years; or have central nervous system metastases or carcinomatous meningitis. Documentation of a negative serum human chorionic gonadotropin pregnancy test must be available for premenopausal women of reproductive capacity and for women less than 12 months after menopause. Patients with medical or psychiatric disorders that would interfere with informed consent or make them a poor risk for participation in this trial, and who are currently using or planning to use other investigational therapy or any other anticancer therapy, are also ineligible.

**Treatment Plan**

Oxaliplatin will be administered as a 2-hour intravenous infusion on days 1 and 15 (Table 1). UFT plus oral calcium folinate will be given daily in two divided doses on days 1 through 5, 8 through 12, and 15 through 19: The UFT daily dose will be rounded up or down to the nearest 100 mg, and given in divided doses twice a day. If the total number of capsules a patient is to receive in one day cannot be divided equally, the highest dose will be given in the morning. A 30-mg dose of oral calcium folinate will be administered concurrently with each dose of UFT. Patients should not consume any food for 1 hour prior to and 1 hour following the ingestion of UFT plus oral calcium folinate. Courses will be repeated every 28 days in the absence of disease progression or unacceptable toxicity. At least three patients will be studied at each dose level and each will complete one course (28 days) before proceeding to the next dose level (Table 1). At each dose level, the first patient entered will be observed for at least 4 weeks (28 days) prior to the entry of subsequent patients. Dose escalations are not permitted in individual patients.

If none of the initial three patients treated at a given dose level develop dose-limiting toxicity, dose escalation will continue (Table 2). If one of the initial three patients treated develops dose-limiting toxicity, then three additional patients will be entered on the same dose level. If none of the three additional patients treated at the same dose level develop dose-limiting toxicity, dose escalation will continue. If two or more of the initial three patients treated on a dose level or one or more of the additional three patients treated on a dose level develop dose-limiting toxicity, dose escalation will cease. Up to nine patients may be treated at a given dose level to ensure that the maximum tolerated dose criteria are met before declaring that dose level the maximum tolerated dose (the highest dose level that does not cause dose-limiting toxicity in more than one patient). Dose-limiting toxicity is unacceptable toxicity within the first course of therapy, defined as grade ≥ 3 nausea, vomiting, or diarrhea, uncontrolled by aggressive antiemetic or anti-diarrheal support; grade 4 neutropenia or leukopenia that persists for > 3 days or febrile neutropenia defined as a temperature ≥ 38.5°C and an absolute neutrophil count < 1,000/µL; grade ≥ 3 hematologic toxicity with the exception of neutropenia and leukopenia; grade ≥ 3 other toxicity including gastrointestinal, renal, cardiac, pulmonary, hepatic, and neurologic toxicity; or inability of the patient to take ≥ 75% of the planned UFT plus oral calcium folinate dose.

Responses will be graded according to the World Health Organization guidelines.[20] Tumor status will be evaluated after two courses of therapy (8 weeks). Patients with progressive disease will
discontinue protocol treatment. Responding or stable patients may continue to receive this therapy until disease progression as long as the toxicity profile is acceptable. Patients with evaluable but nonmeasurable disease, defined as disease that cannot be measured in conventional fashion but can be evaluated for tumor response, are eligible for this study.

Summary

The combination of oxaliplatin with UFT and oral calcium folinate is based on the impressive results obtained with the combination of oxaliplatin and 5-FU in advanced colorectal cancer. Phase III trials comparing 5-FU plus oral calcium folinate regimens with or without oxaliplatin demonstrated near doubling of response rates and significant impact on time to disease progression with the addition of oxaliplatin. In addition to patient convenience, UFT plus oral calcium folinate also offers advantages over intravenous 5-FU-based regimens. UFT plus oral calcium folinate has been shown to produce therapeutic efficacy similar to 5-FU plus oral calcium folinate with a marked reduction in toxicities, such as grades 3 and 4 neutropenia and mucositis. It can provide sustained levels of 5-FU, similar to those achieved with protracted intravenous 5-FU infusions, without technical complications such as line sepsis and thrombosis. UFT plus oral calcium folinate has been examined in the adjuvant setting of colon cancer in a large, randomized National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, which completed accrual in March 1999. The subsequent adjuvant trial (NSABP CO-7) will compare a weekly 5-FU plus oral calcium folinate regimen against the same regimen plus oxaliplatin. The trial described herein, which combines oxaliplatin and UFT and oral calcium folinate, will hopefully provide the basis for evaluation of this regimen in the metastatic setting, as well as in potential future adjuvant trials.

References:


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