Preoperative UFT and Calcium Folinate and Radiotherapy in Rectal Cancer

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Protracted infusions of 5-fluorouracil (5-FU) combined with pelvic radiotherapy have been associated with improved survival and decreased local and distant metastases in the adjuvant therapy of rectal cancer. However,

Introduction

A combination of the agents UFT and calcium folinate is known as Orzel. UFT is an oral anticancer drug composed of a fixed molar ratio (4:1) of uracil and tegafur. In vivo, tegafur, acting as a prodrug, is metabolized to release the antineoplastic agent 5-fluorouracil (5-FU). Uracil is combined with tegafur to act as a competitive inhibitor of dihydropyrimidine dehydrogenase, the primary catabolic enzyme for 5-FU.[1-3] Competitive inhibition of dihydropyrimidine dehydrogenase by uracil results in elevated and sustained concentrations of 5-FU, which is derived from tegafur, in the plasma and higher intratumoral exposure to cytotoxic 5-FU anabolics as compared with tegafur administered alone.[4,5] Administration of calcium folinate along with UFT may provide additional antitumor efficacy, comparable with the efficacy previously demonstrated with intravenous 5-FU plus calcium folinate regimens.[6]

The ability of repeated doses of UFT to provide consistently low concentrations of 5-FU in the plasma suggests that UFT could be an important compound for the treatment of gastrointestinal malignancies.[7] In addition to promising efficacy data, there is a wealth of clinical experience demonstrating a highly acceptable safety profile for UFT. The dose-limiting side effect associated with UFT when administered in protracted schedules is diarrhea.[8]

With demonstrated improvement in local control and possibly in survival, rectal cancer patients have been routinely treated with a combination of 5-FU and radiotherapy, given either before or after surgery.[9] Based on encouraging results of preoperative chemoradiation trials,[10-12] and the potential for sphincter preservation, preoperative chemoradiation is used at The University of Texas M. D. Anderson Cancer Center for patients with rectal neoplasms (T3 and T4, nodal involvement, or both).

Pharmacokinetic trials comparing 5-FU levels attained from UFT to those observed with low-dose protracted intravenous infusions have demonstrated a similar area under the curve, with higher 5-FU peak levels associated with UFT administration.[13] Protracted intravenous and bolus 5-FU administration, both in combination with pelvic radiotherapy, have been compared, with the conclusion that protracted intravenous 5-FU infusions provide superior survival, and local and distant control of disease. Nevertheless, protracted intravenous infusions are associated with the expense of central venous catheter insertion, infusion pump maintenance, and the cost associated with treatment complications (line infections, thrombosis, slippage). An oral delivery system allowing protracted 5-FU delivery would be advantageous from a patient comfort, expense, and safety viewpoint.

A large, randomized trial comparing UFT plus oral calcium folinate to intravenous 5-FU plus calcium folinate in previously untreated metastatic colorectal cancer demonstrated equivalent survival with clinically significant safety advantages to the UFT plus oral calcium folinate arm. Although UFT plus oral calcium folinate has been administered to a large number of patients, relatively limited information regarding the combination of this agent with radiotherapy is currently available. The primary goal of our present trial is to investigate the antitumor efficacy and safety of a preoperative regimen of UFT plus oral calcium folinate combined with radiotherapy in patients with rectal cancer. The use of UFT plus oral calcium folinate in this setting might prove to be a less toxic...
and more cost-effective and convenient treatment for patients with rectal cancer than protracted intravenous 5-FU infusions or bolus 5-FU plus calcium folinate.

**Patient Eligibility**

Patients must have a histologically confirmed diagnosis of rectal cancer for which chemotherapy and pelvic irradiation are indicated, such as patients with endoscopic evidence of T3 and T4 lesions, nodal involvement, or both. Patients also must be able to tolerate major surgery. Other eligibility criteria include age over 18 years; an Eastern Cooperative Oncology Group performance status of 0 to 2; normal renal, hepatic, and hematologic function; and a life expectancy > 3 months. Patients with distant metastasis or prior malignancies other than localized, treated nonmelanoma skin cancer and cervical cancer are ineligible. In addition, women who are pregnant or nursing and patients who have undergone a major surgical procedure within 3 weeks before enrollment are ineligible. Patients must sign an informed consent form indicating that they are aware of the investigational nature of the study.

Prior to entering the study, all patients are required to have a complete medical history and physical examination, including documentation of the presumed stage of disease, performance status, and concurrent nonmalignant diseases and prior treatments. Baseline laboratory studies include a complete blood count with differential and platelet count, electrocardiogram, chest x-ray, electrolytes, carcinoembryonic antigen level, SMA-12, and urinalysis. Prior to each treatment course, physical examination and laboratory tests are repeated. A complete blood count is obtained weekly during each course. Patients found to have metastatic disease after enrollment are removed from the study but are considered evaluable for toxicity.

**Treatment**

Each group of three patients receives an escalating dose of oral UFT (starting at 250 mg/m²/day) and a fixed dose of oral calcium folinate (90 mg/day), both administered in three divided doses daily for 5 consecutive days. Table 1 shows the UFT dose-escalation schedule. Radiotherapy is given to the pelvis at 180 cGy/day once a day on the same 5 days that UFT and calcium folinate are administered. The patient then rests for 2 days. This 7-day cycle (5 days of treatment, 2 days of rest) is repeated four additional times for a total of 5 weeks of treatment. Over the 5 weeks, 4,500 cGy of radiation is administered. Surgical resection is performed 4 to 6 weeks after this combination of chemotherapy and radiotherapy. Four weeks later, all patients receive fixed doses of UFT (300 mg/m²/day) and calcium folinate (90 mg/day) three times a day for 28 consecutive days, followed by a 7-day rest period, as previously recommended.[8] This 35-day cycle is repeated for a total of four cycles. At level 0, the postoperative dose of UFT is limited to 250 mg/m²/day. UFT and calcium folinate are administered in 100-mg capsules and 15-mg tablets, respectively. Because the available capsule dose of UFT is 100 mg (based on tegafur), the total daily dosage is approximated to the nearest 100 mg. If the number of capsules per day cannot be evenly distributed between the three daily doses, the greater capsule count is administered in the morning and afternoon, and the lower number is taken in the evening. Patients are instructed to take UFT and calcium folinate 1 hour after meals.

Patients are contacted by telephone at weekly intervals by a research nurse to monitor therapy-related toxicity. Patient compliance is verified at the end of each cycle by verifying the remaining medication and by reviewing patient diaries. Standard antiemetic therapy is prescribed as required. Prophylactic antidiarrheal drugs are not allowed. However, if grade ≥ 2 diarrhea develops, brief courses of antidiarrheals can be used for symptomatic relief. Weekly toxicity notations are made and are graded as per the National Cancer Institute Common Toxicity Criteria. The days when treatment is withheld because of toxic effects are counted as treatment days and are not made up. Therapy is withheld upon development of diarrhea, mucositis, stomatitis, and any other nonhematologic toxicity with a Common Toxicity Criteria grade ≥ 2. Therapy is resumed when the toxic event and associated symptoms are completely resolved. Before initiation of subsequent cycles of UFT plus oral calcium folinate, all nonhematologic toxicities must be Common Toxicity Criteria grade ≤ 1. Dosage modifications of UFT at the start of a new cycle are based on the worst Common Toxicity Criteria grade nonhematologic toxicity encountered during the preceding cycle of chemotherapy or the nadir granulocyte and platelet counts during the preceding cycle of therapy. A minimum of three patients must be enrolled in each cohort before dose escalation is allowed. If one patient has grade ≥ 3 toxicity, three more patients are entered at the same dose level. If two of six patients have grade ≥ 3 toxicity, the escalation continues; but if three of six patients have grade ≥
3 toxicity, the next cohort is entered at a lower dose level. If no additional dose-limiting toxicity is observed in the patients treated at the reduced level, this dose is recommended as the maximum tolerated dose.

**Results and Discussion**

Eleven patients have been entered in this trial. Dose escalations to UFT 350 mg/m²/day have been performed. Diarrhea is the predominant toxicity at this dose level, but is adequately controlled with the use of conventional antidiarrheal agents, allowing completion of pelvic irradiation and UFT plus oral calcium folinate administration on schedule. This trial demonstrates that even with pelvic radiotherapy administration, adequate daily doses of UFT can be administered. When given at this dose level, UFT can achieve 5-FU plasma levels similar to those achieved with protracted infusions of intravenous 5-FU, which are commonly used with pelvic irradiation. This intermittent schedule of UFT plus oral calcium folinate (5 days of treatment followed by 2 days of rest) allows for a normal tissue rest period and for greater tolerability with a higher daily dose of UFT. Dose escalations of UFT plus oral calcium folinate will continue in this trial.

**References:**


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