Preoperative UFT/Leucovorin and Radiation Therapy in Rectal Cancer

Introduction

In the year 2000, approximately 36,400 patients in the United States will be diagnosed with rectal cancer. Despite surgical resection, a significant number of these patients will be candidates for further adjuvant treatments. Since the 1980s, the role of postoperative pelvic radiation and fluorouracil (5-FU)-based chemotherapy for patients with stages II and III adenocarcinomas of the rectum has become well established. Continuous infusion 5-FU has proven to be superior to bolus 5-FU schedules when given during radiation. The modulation of 5-FU by leucovorin produced increased response rates in metastatic colorectal cancer patients. However, the results were similar for patients with rectal cancer undergoing postoperative radiation with bolus 5-FU alone or in combination with leucovorin (calcium folinate), levamisole (Ergomisol), or both. The optimal timing as well as the optimal regimen for the adjuvant treatment of rectal cancer remains unclear. Over the past few years, a considerable number of oral fluoropyrimidines have been investigated for the treatment of colorectal cancer. Oral fluoropyrimidines represent an attractive and convenient alternative to intravenous 5-FU. In addition, oral chemotherapy may circumvent the problems and costs associated with central venous lines and portable infusion pumps.

UFT/Leucovorin

Tegafur is a prodrug converted to 5-FU by the hepatic microsomal system. It was initially evaluated in the 1970s by the National Cancer Institute. Studies of intravenous tegafur demonstrated objective responses in solid tumors, but the severe toxicity halted its development in the United States. Japanese researchers, on the other hand, took advantage of the drug’s good oral bioavailability, and split the oral dosing, which led to a significant improvement in its toxicity profile. Objective responses were then observed in a variety of solid tumors. Further research produced the combination of uracil with tegafur (UFT), in a fixed molar ratio of 4:1. Uracil is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), the chief catabolic enzyme of 5-FU. The inhibition of DPD by uracil results in elevated and well-maintained concentrations of 5-FU. Preclinical experiments confirmed that leucovorin combined with UFT has enhanced antitumor activity. This combination is currently undergoing evaluation in various solid tumors.

UFT plus oral leucovorin (a combination being developed under the trade name Orzel) has been investigated in the treatment of advanced colorectal cancer, and has produced objective response rates ranging from 25% to 42%. Preliminary results from two large randomized studies in patients with metastatic colorectal cancer suggest that UFT plus leucovorin may be equivalent to bolus 5-FU plus leucovorin in terms of response rates and survival. UFT plus leucovorin is generally well tolerated, with diarrhea, nausea, and anorexia being the most frequent adverse events. Grade 3 or 4 diarrhea was observed in 4% to 21% of patients. However, UFT plus leucovorin is not associated with significant myelosuppression, mucositis, hand-foot syndrome, or alopecia.

Preoperative UFT/Leucovorin in Rectal Cancer

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The use of combined modality regimens has been well established in the treatment of stages II and III rectal cancer. The most common chemotherapy regimens used include continuous-infusion 5-FU delivered with the help of a central venous catheter and the use of portable pumps.
Based on the encouraging results reported from trials of preoperative (neoadjuvant) chemoradiation trials,[15-17] this treatment modality is routinely used at The University of Texas M. D. Anderson Cancer Center for patients with stages II and III rectal cancer. Advantages associated with preoperative adjuvant therapy include an in vivo evaluation of drug efficacy, an intact blood supply to the tumor, and a reduced amount of small bowel in the radiated field. In addition, the potential for sphincter preservation with this approach represents a major advantage. The main disadvantage of preoperative therapy is its limited ability to stage the tumor pathologically. Pharmacokinetic studies comparing 5-FU levels obtained with protracted infusions of 5-FU with those obtained with oral UFT have demonstrated a similar area-under-the-curve for both agents, with higher peak levels of 5-FU associated with UFT.[11] Although UFT plus leucovorin has been administered to many patients, relatively little is known about the combination of these agents and radiation for rectal cancer. The primary goal of our ongoing trial is to investigate the antitumor efficacy and safety of a preoperative regimen of UFT plus leucovorin combined with radiation in patients with rectal cancer. This regimen might prove to be less toxic, more cost-effective, and a convenient adjuvant treatment for these patients.

**Patient Eligibility and Pretreatment Evaluation**

Patients with histologically confirmed rectal cancer for whom adjuvant chemotherapy and radiation are indicated (ie, those with T3 or T4 lesions, or nodal involvement as evidenced by endoscopy) are eligible for the study. Other eligibility criteria include the ability to tolerate major surgery, age over 18 years, Zubrod performance status of 0 to 2, normal renal, hepatic, and hematologic functions, and a life expectancy > 3 months. Patients with distant metastasis or prior malignancies, those who have had major surgery within the previous 3 weeks, and pregnant or nursing women are ineligible. Written informed consent must be provided prior to study enrollment. A complete medical history and physical examination are obtained at baseline, and all patients undergo a complete blood count, chemistry profile including liver and renal function tests, electrocardiogram, chest radiograph, serum level of carcinoembryonic antigen, and urinalysis. Complete blood counts are obtained weekly throughout treatment.

**Treatment Program**

Each group of three patients receives an escalating dose of oral UFT (starting at 250 mg/m²/d) and a fixed dose of oral leucovorin (90 mg/d), both of which are administered in three daily doses for 5 consecutive days. Table 1 presents the UFT dose-escalation schedule. Radiation therapy is delivered to the pelvis in daily fractions of 180 cGy on the same 5 days as the chemotherapy is administered. A 2-day rest follows, then the 7-day cycle is repeated for a total of 5 weeks. The total dose of radiation is 4,500 cGy. Surgical resection is performed 4 to 6 weeks after the completion of chemoradiation. Four weeks after surgery, patients receive fixed doses of UFT (300 mg/m²/d) and leucovorin (90 mg/d) in three daily doses for 28 consecutive days, followed by a 7-day rest period, as previously recommended.[18] This 35-day cycle is repeated four times. At dose levels 0, [1], and [2], the postoperative dose of UFT is 250 mg/m²/d. Figure 1 outlines the overall treatment plan. Standard antiemetic therapy is prescribed as required. Antidiarrheal drugs are not allowed prophylactically, but may be used for symptomatic treatment of grade 2 or higher diarrhea. Toxicity is recorded weekly according to the National Cancer Institute Common Toxicity Criteria. If grade 2 or higher toxicity develops, therapy is halted and not resumed until all symptoms have completely resolved. Days lost due to withheld therapy are not made up and are counted as treatment days. This phase I trial follows the usual [3 plus 3] method, where cohorts of three patients are entered at each dose level. If two or three of the patients in dose level 0 develop grade 3 or 4 toxicity, a new cohort is treated at the lower dose level. If zero or one patient develops grade 3 or 4 toxicity, three more patients are treated at the same dose level. If up to two of six patients develop grade 3 or 4 toxicity, escalation continues. If three or more patients develop grade 3 or 4 toxicity, the next cohort of three patients is entered at the next lower dose level. The maximum tolerated dose is the dose level that is immediately below the one producing dose-limiting toxicity in two or more of three patients, or three or more of six patients.

**Preliminary Results and Conclusions**

As of this writing, 11 patients have been entered into this trial. Dose escalation of UFT up to 350
mg/m2/d has been achieved. Diarrhea is the predominant toxicity at this level, but is adequately controlled with conventional antidiarrheal agents. Both chemotherapy and pelvic radiation could be completed on schedule in all patients. This phase I study will determine the tolerability of a preoperative, combined-modality, adjuvant treatment that includes UFT plus leucovorin and radiation therapy. The potential for sphincter preservation and the convenience of oral chemotherapy make this approach an attractive alternative in the adjuvant treatment of patients with rectal cancer that is penetrating through the bowel wall or involving regional lymph nodes. Further studies are necessary to better define the role of preoperative chemoradiation in rectal cancer, especially in terms of its comparability to 5-FU-based, postoperative, adjuvant chemoradiation.

References:


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