Postoperative Radiation Therapy for Rectal Cancer Combined With UFT/Leucovorin

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Postoperative combined-modality therapy with fluorouracil (5-FU) and radiation therapy is accepted practice for high-risk rectal cancer. Postoperative pelvic radiotherapy alone may improve pelvic control, but is not associated with an improvement in survival.

Introduction

Standard postoperative therapy in the United States for transmural or node-positive rectal adenocarcinoma is chemotherapy and pelvic radiation.[1] Postoperative radiation therapy alone may improve local control, but has no impact on survival.[2] However, the addition of concurrent fluorouracil-based chemotherapy to radiotherapy has been shown to improve tumor control and prolong survival compared to surgery alone[3] or radiation alone.[4] Intergroup postoperative trials have focused on identifying the most effective chemotherapeutic agents and dose schedule when combined with radiotherapy.

The major focus of postoperative trials has been on the role of semustine (MeCCNU), the modulation of fluorouracil (5-FU) with leucovorin and/or levamisole, and the comparison between bolus and infusional 5-FU. Semustine does not improve local control or survival, so it is no longer recommended for use in the adjuvant treatment of rectal cancer.[5,6]

Single and Combination 5-FU

Intergroup trial 0114 evaluated single-agent 5-FU and three combinations of modulated fluorouracil chemotherapy (5-FU plus leucovorin, 5-FU plus levamisole, and 5-FU/leucovorin/levamisole) combined with postoperative adjuvant radiotherapy for rectal cancer. All patients received six cycles of postoperative adjuvant chemotherapy, with radiotherapy given during cycles 3 and 4. There was no significant difference in local control or survival among the four arms at a median 4-year follow-up.[7] The total grade ≥ 3 toxicity was also similar, but there were differences in the types of toxicity among arms.

Single-agent 5-FU had more hematologic toxicity, and 5-FU plus levamisole had more diarrhea. Gender differences in toxicity were noted: women had a significantly greater incidence of grade ≥ 3 toxicity in all arms without clear explanation. These data suggest that there is no routine role for levamisole, but conditional probability analysis demonstrated that the addition of leucovorin might be an advantage on longer follow-up, despite the fact that many expected recurrences had already occurred by the time of analysis.

Bolus vs Infusional 5-FU

Bolus vs infusional 5-FU administered concurrently with postoperative radiotherapy was evaluated in the Mayo Clinic and North Central Cooperative Trial Group (NCCTG) 86-47-51 study.[5] In this trial, bolus 5-FU was compared to continuous-infusion 5-FU during radiation. Infusional therapy was associated with a significant decrease in overall relapse (47% vs 37%, P = .01), distant metastases (31% vs 40%, P = .03), and an improvement in 4-year survival (70% vs 60%, P = .005).[5] These data suggest that single-agent 5-FU is more effective when administered as a continuous infusion rather than given as a single-agent bolus when combined with postoperative radiotherapy.

It is important to note that these actual and disease-free survival results with infusional 5-FU are very similar to those found with bolus 5-FU plus leucovorin in the Intergroup 0114 trial.[7] Present data do not allow us to compare continuous-infusion 5-FU with bolus 5-FU plus leucovorin; both are considered to be acceptable regimens in practice during postoperative adjuvant radiotherapy for rectal cancer. An Intergroup study is ongoing to clarify further optimum adjuvant therapy.

Toxicities of concurrent radiotherapy and continuous-infusion vs bolus 5-FU were different. Infusional
therapy led to a significant increase in grade ≥ 3 diarrhea (24% vs 14%, P > .01), but there was a decrease in grade ≥ 3 neutropenia (2% vs 11%, P > .01). On the basis of improved overall survival in this prospective randomized setting, however, many investigators consider infusional 5-FU during radiation to represent standard practice.

Practical considerations of 5-FU infusional therapy include patient acceptance, labor intensity, requirement for prolonged venous access, external pump cost and maintenance. Prolonged venous access has been associated with the risk for line infection and venous thrombosis.[8] If an equally effective oral agent were to replace infusional 5-FU, it would have the potential to increase convenience and may be less labor-intensive.

Other new chemotherapy agents in development or approved by the Food and Drug Administration (FDA) for colorectal cancer include irinotecan (Camptosar, CPT-11), raltitrexed (Tomudex), trimetrexate (NeuTrexin), oxaliplatin, and several oral fluoropyrimidine prodrugs. Capecitabine (Xeloda) is absorbed unmodified from the gut and subsequently metabolized to 5-FU.[9]

Ethynyluracil (Eniluracil) is an inhibitor of dihydroyridine dehydrogenase (DPD), and is combined with oral 5-FU.[10] BOF-A2 is a 5-FU prodrug combined with another inhibitor of 5-FU metabolism, 3-cyano-2,6-dehydropyrimidine (CNDP).[11] S-1 combines tegafur with two inhibitors of 5-FU catabolism, namely oxonic acid and 5-chloro-2,4-dihydropyridine (CDHP).[12]

Tegafur is an oral prodrug that is converted to 5-FU in vivo. Uracl enhances the concentration of 5-FU by inhibiting DPD-mediated 5-FU catabolism.[13] The combination of oral leucovorin and UFT (uracil and tegafur) is being developed under the trade name Orzel. The leucovorin additionally modulates cytotoxicity by increasing the pool of reduced folate required as part of a covalent ternary complex with thymidylate synthase and fluorodeoxyuridine 5´-monophosphate.[14-16]

The clinical rationale for combining leucovorin and UFT is the same as the advantage in terms of objective tumor response for the combination of leucovorin with intravenous bolus 5-FU over 5-FU alone. UFT is commercially available in Japan and has been used extensively as an alternative to 5-FU.[17] UFT has been under development in the United States since the early 1990s. The recommended phase II dose is 300 mg/m²/d, but it has been tolerated at even higher doses.[18]

**UFT/Leucovorin Trials**

There have been two phase III trials comparing UFT plus leucovorin with bolus 5-FU plus leucovorin in stage IV colorectal cancer. In trial 001, patients received either UFT 300 mg/m²/d with leucovorin 75 mg/d for 5 days per week for a total 28 days, or 5-FU 425 mg/m²/d and leucovorin 20 mg/m²/d for 5 days every 4 weeks.[19] This international trial accrued 816 patients. There were no significant differences in overall survival or response rate.

There was an improved toxicity profile for UFT in reduction of neutropenia, febrile neutropenia, nausea, emesis, and diarrhea. Common Toxicity Criteria grade 3/4 mucositis was reduced from 19% to 1% (P > .001). A confirmatory trial (012), with a similar design, led to the same conclusion.[20]

These data suggest that UFT plus leucovorin is a well-tolerated, fully oral treatment for patients with metastatic colorectal cancer with efficacy comparable to intravenous 5-FU. Because pelvic radiation toxicities include proctitis and diarrhea, a fluoropyrimidine regimen with less overlapping toxicity would be preferable during pelvic radiotherapy. Additionally, a daily oral regimen has the potential to mimic the pharmacokinetics of an infusion, which would allow for administration of fluoropyrimidine therapy at the optimal dose schedule before, during, and after radiation.

An ongoing phase I trial was originated at the Memorial Sloan-Kettering Cancer Center to determine the maximum tolerated dose of UFT plus leucovorin, and dose-limiting toxicity when given concurrently with pelvic radiotherapy for patients with resected rectal cancer. This trial has recently been open to accrual at the University of Pennsylvania Cancer Center.

Patients with histologically confirmed, resected rectal adenocarcinoma and with adequate performance status and renal, hepatic, and hematologic reserve are eligible for the study if the tumor has transmural spread and/or nodal metastases. Radiation therapy consists of three- or four-field ≥ 10 megavolt (MV) photons directed to the pelvis at 1.8 Gy/d to 45 Gy/5 weeks with a tumor bed boost to 50.4 Gy.

UFT is administered orally three times per day, 7 days per week for each 28-day cycle. The drug is available in nondividable 100-mg capsules. Individual doses are rounded to the nearest 100 mg. Leucovorin at a fixed dose of 30 mg is also taken orally three times a day with UFT.

Five 28-day cycles of UFT plus leucovorin are given. Cycle 1 is started within 10 weeks from surgery, with all patients receiving the known maximum tolerated dose of 300 mg/m²/d of UFT (when given alone) plus leucovorin. Pelvic radiation is begun on day 35, after a 1-week break, along with cycle 2.
UFT plus leucovorin. The starting dose given with radiation was 175 mg/m²/d, and UFT is escalated in patient cohorts at 50 mg/m²/d increments. Postradiation cycle 3 starts after a 3-week rest, and cycles 4 and 5 start after 1-week rests as summarized in Figure 1.

**Discussion**

Others have combined UFT plus leucovorin with pelvic radiotherapy for rectal cancer. The group from the M. D. Anderson Cancer Center is performing a trial in which UFT plus leucovorin is combined with preoperative radiotherapy for rectal cancer.[21] A group from Spain has recently reported their experience with UFT plus leucovorin with pelvic radiotherapy for unresectable or recurrent rectal cancer. Thirty-five patients received 45 Gy pelvic radiation therapy with UFT at 300 mg/m²/d plus leucovorin at 30 mg/d.[22] Fifteen of 22 (68%) patients with unresectable cancer were able to have resections, and there was a complete pathologic response in three cases. Eight of 35 (23%) had grade 3 diarrhea. That incidence of grade 3 diarrhea is similar to the 24% incidence reported in the Mayo/NCCTG 86-47-51 study. This suggests that daily oral UFT plus leucovorin may be at least as active and also as well tolerated as infusional 5-FU when given during radiation. It should be recognized that UFT plus leucovorin was given at full recommended dose as a single agent, in contrast to the protracted infusion of 5-FU, which was given at a dose of 225 mg/m²/d in the Mayo/NCCTG study.[5] This dose is less than the dose of 250 to 300 mg/m²/d typically used in protracted venous-infusion fluorouracil without radiation therapy.

Oral administration obviates the need for venous access and its associated complications. These potential advantages must, however, be weighed against potential disadvantages, such as variable gut absorption in some patients[23,24] and patient compliance. Compliance with oral oncology agents has been reported to be excellent in many[25,26] but not all[27] trials. A survey of 103 chemotherapy-naive patients with newly diagnosed metastatic cancer found that 89% of patients preferred an oral over an intravenous regimen, as long as it was equally effective.[28] Reasons cited for preference included convenience, lack of intravenous access, control of the treatment environment, and travel issues. Only a minority of patients, however, would accept an oral regimen with a lower or less durable response. Some have presumed that an oral chemotherapy regimen would result in an improved quality of life, but this has not been studied prospectively.

The current phase I trial of UFT plus leucovorin combined with postoperative radiation therapy for rectal cancer is continuing. Other investigators are also performing phase I trials with UFT plus leucovorin and radiotherapy for other tumor types. The group from the University of Alabama Medical Center[29] is combining UFT plus leucovorin with radiotherapy in patients with both resected and unresected pancreatic cancer.

**Conclusion**

Previous studies in patients with stage IV colorectal cancer randomized to UFT versus parenteral 5-FU confirm equal efficacy, with significantly less mucositis and diarrhea. A potential therapeutic advantage for UFT plus leucovorin is the apparent reduction in overlapping toxicities when combined with pelvic radiation. Results of one completed study suggest that response rates and toxicities of UFT plus leucovorin are at least comparable to infusional 5-FU when combined with definitive or preoperative pelvic radiotherapy for rectal cancer. A survey has shown that most cancer patients would prefer an equally effective oral chemotherapy regimen. An oral fluoropyrimidine regimen has the potential to mimic the pharmacokinetics of a continuous infusion. UFT plus leucovorin is an attractive alternative to either bolus or continuous-infusion 5-FU combined with postoperative pelvic radiotherapy for rectal cancer. Accrual to this study is ongoing.

**References:**


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