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Clinical report

Phase I study of oral uracil and Tegafur plus leucovorin and pelvic radiation in patients with recurrent rectal cancer

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Continuous 5-fluorouracil (5-FU) infusion during radiation therapy is superior to the application of bolus 5-FU schedules. As an oral therapy, that provides prolonged fluoropyrimidine exposure, uracil and Tegafur (UFT) plus leucovorin (LV) has shown favorable activity with only moderate toxicity in colorectal cancer. The present study was designed to evaluate the safety of UFT + LV combined with pelvic radiation to determine the maximum-tolerated dose (MTD) in recurrent rectal cancer. Patients with recurrent rectal cancer received escalating doses of UFT (starting at 250 mg/m^2/day with 50 mg/m^2/day increments between consecutive cohorts) and fixed doses of LV (90 mg). The UFT + LV combination was given 5 days per week simultaneously to a 5-week course of irradiation up to a total dose of 50.4 Gy, 1.8 Gy daily fractions followed by a boost of 5.4 or 9.0 Gy to the gross tumor volume. Nineteen patients were treated and 14 received the full chemotherapy with delivery of all planned radiotherapy. The MTD of UFT was 400 mg/m^2/day due to the occurrence of dose-limiting diarrhea and emesis. Toxicities were mild and manageable on the lower dose levels. Treatment was feasible mainly on an outpatient base. We conclude that combined chemoradiation with oral UFT + LV is feasible and well tolerated for recurrent rectal cancer patients undergoing pelvic radiation. The safety profile appears comparable to that of i.v. dosing without requiring any i.v. port systems. The recommended doses for further phase II chemoradiation trials are 350 mg/m^2/day UFT + 90 mg LV. [© 2002 Lippincott Williams & Wilkins.]

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Introduction

5-Fluorouracil (5-FU)-based combined modality treatment for rectal cancer has been established as an integral part for the (neo-)adjuvant setting and is also used for recurrent disease.

Treatment failures result from both local disease recurrence and distant metastatic spread. Pelvic irradiation can decrease local recurrence in patients with clinically resectable T3 and/or N1–3, M0 disease. The addition of systemic 5-FU-based chemotherapy further enhances local control and improves overall survival.[1]

Treatment options for recurrent rectal cancer depend on the nature of previous treatment, the general condition and the life expectancy.

Radiotherapy is used to diminish symptoms such as pain and hemorrhage, and results in improved local control. In unresectable cases combined chemoradiation offers symptom control and may improve survival rates also. In a series from the Mayo Clinic 65 patients with locally unresectable recurrent colorectal cancer were assigned to receive either radiotherapy and 5-FU or radiotherapy and placebo. Median survival was 10.5 months in the placebo group versus 16 months in the 5-FU group.[2,3]

More recently, new chemotherapeutic agents, either in clinical development or already approved, are being evaluated in place of 5-FU in the combined modality treatment.

Uracil and Tegafur in a molar ratio of 4:1 (UFT) plus calcium folinate comprise the components of the oral agent Orzel.

Continuous 5-FU infusion during radiation therapy is superior to the application of bolus 5-FU schedules.[4] As an oral therapy, that provides prolonged fluoropyrimidine exposure, mimicking continuous infusion of 5-FU, UFT plus leucovorin (LV) has shown favorable activity with only moderate toxicity in colorectal cancer.[5,6]

The present study was designed to evaluate the safety of UFT + LV combined with pelvic radiation to determine the maximum-tolerated dose (MTD) by describing the dose-limiting toxicity (DLT) in recurrent rectal cancer.

Patients and methods

Patients, 18 years and older, with recurrent rectal cancer were eligible for the study, if histologically proven relapsing tumor was inoperable and provided for primary radio-chemotherapy. Further eligibility requirements included: a performance status $\leqslant 2$ according ECOG criteria, a projected life expectancy $\geqslant 3$ months, adequate renal and liver organ function, adequate hematological function with a white blood count $>4000/\mu l$, and a platelet count of $>100\,000/\mu l$, no prior radiotherapy, no previous treatment with 5-FU and/or 5-FU analogs within the last 6 months, localized disease without dissemination, and no previous history of malignant disease within 5 years of study entry other than skin or cervical cancer. Patients suffering from any known cardiac disease were excluded. The study was approved by the institutional ethical review boards and all patients gave written informed consent.[7]

Primary endpoint was the assessment of the MTD dose by describing the DLT caused by a dose-escalating schedule of UFT + LV orally administered, simultaneously to pelvic radiation.

Patients received escalating doses of UFT (starting at $250\,mg/m^2$/day with $50\,mg/m^2$/day increments between consecutive cohorts) and fixed doses of LV (90 mg).

Treatment with oral UFT began concurrent to radiotherapy. The agent was administered 3 times per day through 5 days, or longer, if radiation boost was applied.

The dose of UFT was escalated stepwise (Table 1) in cohorts of three or more patients, based on toxicity. If a DLT was observed in at least one of three patients at any dose level, the cohort was expanded to six patients. The next dose level was started, if no more than two of six patients suffered from dose-limiting side effects. Once the MTD has been determined, the following patients were treated at this dose level to further evaluate toxicity rates.

DLT was graded using the Common Toxicity Criteria (CTC) scale. The MTD for UFT plus calcium folinate administered with radiation therapy was defined for any hematologic and non-hematologic toxicity as value of 3 or worse with the exception of alopecia, nausea, vomiting or diarrhea. Grade 4 vomiting and diarrhea or gastrointestinal toxicity more than grade 2 requiring treatment interruption of at least 7 days or the inability of the patient to take more than 75% of the planned chemotherapy dose during treatment period were further defined as being DLT criteria.

The radiation treatment was performed with linear accelerators (minimum energy 10 MV) using an isocentric box technique. To spare as much bowel as possible, lateral and anterior fields were applied to treat the pelvic region. The small bowel was displaced out of the pelvis by prone patient positioning using a belly board. The primary tumor volume, internal iliacal and presacral lymph nodes were included in the planning target volume. Thereafter, a smaller boost field was administered to treat the primary tumor site.

The UFT + LV combination was given 5 days per week simultaneously to a 5-week course of irradiation up to a total dose of 50.4 Gy, 1.8 Gy daily fractions followed by a boost of 5.4 or 9.0 Gy.

Patients were monitored weekly in regard of tolerance, side effects and blood count. Clinical response was evaluated by computed tomography.

Results

A total of 19 patients were treated. Median age was 61.1 years (range 48–76 years); 4 patients were female and 15 male. According to the inclusion criteria performance status was 1 or better graded by the ECOG scale, 12 out of 19 patients were defined as ECOG 0. Prior to initiation of therapy the tumor volume was measurable by pelvic computed tomography in 15 of 19 patients.

Table 1. Dose escalation during chemotherapy

Dose level	UFT (mg/m^2/day)	Calcium folinate (mg/day; absolute)
1	250	90
2	300	90
3	350	90
4	400	90

Fourteen patients received the full chemotherapy with delivery of all planned radiotherapy; all patients were included in the analysis of toxicity. One patient was removed from study at UFT dose level 1 because of perineal infection requiring secondary surgery. Local tumor progression and subsequent renal dysfunction led to treatment disruption for one patient treated at dose level 2. Chemotherapy was stopped at dose level 4 because of gastrointestinal toxicity grade III lasting more than 7 days in three patients. Both interruptions were not drug related and therefore not graded as being DLT.

The primary toxicity observed was diarrhea, nausea or vomiting. Seven out of 19 patients were hospitalized due to diarrhea and vomiting in three cases; diarrhea less than grade 2 was observed in four of these patients. Chemotherapy was discontinued for 4 days in one patient due to severe diarrhea. Further non-hematologic side effects are listed in Table 2. Myelosuppression was not noted in any case. None of the patients developed grade 4 toxicity.

The MTD of UFT was 400 mg/m^2/day due to the occurrence of dose-limiting diarrhea and emesis. Toxicities were mild and manageable on the lower dose levels. Sixteen patients experienced erythematous skin reactions confined to the treatment portals (CTC grade 2 or below). In particular, cutaneous side effects were not enhanced by the concurrent chemotherapy. None of the patients suffered from hand–foot syndrome. Treatment was feasible mainly on an outpatient base.

Of 14 patients, assessable for response, complete tumor regression was achieved in two cases; a partial response was observed in three patients with an overall response rate of 35,7%. Four out of 14 patients progressed after combined chemoradiotherapy. Table 3 demonstrates the local tumor response in relation to UFT dose level.

Table 2. Acute treatment toxicity

Toxicity (n=19)	CTC grade				
	0	1	2	3	4
Diarrhea	5	3	9	2	0
Nausea/vomiting	13	3	2	1	0
Mucositis	18	1	0	0	0
Fatigue	13	2	4	0	0
Dermatitis	3	9	7	0	0
Hematologic toxicity	19	0	0	0	0

Discussion

The use of pelvic irradiation combined with systemic chemotherapy is effective in reducing the incidence of local recurrence as well as subsequent distant metastasis. The most common chemotherapy schedules include continuous application of 5-FU.[1] Current clinical trials are evaluating various radiation–chemotherapy–surgical interactions as well as the most efficacious chemotherapy program.

Combined modality regimens consisting of chemoradiotherapy are being widely performed in the treatment of locally unresectable, recurrent rectal cancer.[8,9]

The recent availability of oral formulations of 5-FU together with the ability to influence the 5-FU metabolism with LV may improve the efficacy of 5-FU therapy, added to the advantages of a convenient oral regimen. Several oral fluoropyrimidines are under investigation. UFT + oral LV is the first oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine.[10] As reported previously, protracted i.v. 5-FU chemotherapy has been shown to be superior and better tolerated than the i.v. bolus dosing because of prolonged tumor cell exposure to cytotoxic dose levels.[4,11]

The oral administration of UFT (370 mg/m^2) daily simulates continuous infusion of 5-FU (250 mg/m^2) and achieves similar blood concentrations.[12,13] In two multicenter randomized trials in patients with advanced colorectal cancer, UFT + LV produced equivalent activity compared to continuous 5-FU infusion with significantly less toxicity.[6,13] This application form decreases myelotoxic side effects by inhibiting high 5-FU peak levels. The oral application of UFT during most of the radiation course avoids the complications and costs associated

Table 3. Response rates

Dose level	UFT (mg/m^2/day)/LV	Patients (n)	CR	PR	SD	PD	Not measurable
1	250/90	5	2	–	–	1	2
2	300/90	4	–	1	1	1	1
3	350/90	4	–	1	1	1	1
4	400/90	6	–	1	3	1	1
Total			2	3	5	4	5

with the necessity of i.v. catheter or port systems, such as thrombosis or infection.

Previously two phase I/II trials of preoperative multimodality regimens in rectal cancer were conducted, investigating the feasibility of UFT + LV combined with radiation therapy.[14,15] Preoperative radiation therapy plus UFT + LV of stage II and III rectal cancer was evaluated in the phase I study of Hoff *et al.*[16] UFT was administered concurrently to radiation therapy at dose levels between 250 and 350 mg/m^2/day and a fixed dose of LV (90 mg/day). All patients received the planned radiation therapy successfully allowing sphincter-preserving surgery consecutively in 12 of 14 patients.

The phase I/II trial of De la Torre *et al.* investigated unresectable rectal carcinoma patients using combined UFT + LV plus radiotherapy. Comparable to our data, both studies demonstrated DLT at a dose level of 300 and 350 mg/m^2/day UFT, respectively. Equivalent to our results, the predominant side effect was diarrhea, which was generally self-limited and easily managed. Myelosuppression and hand–foot syndrome were rarely noted in this schedules.[14–16]

In the phase II trial of Feliu *et al.*,[17] 28 patients, suffering from locally advanced rectal cancer, were treated preoperatively by radiation therapy concurrently to UFT + LV administered daily at a dose level of 300 or 350 mg/m^2 (days 1–14) and LV 500 mg/m^2 (day 1). DLT grade 3 and 4 consisted of diarrhea, vomiting and mucositis. Consecutively UFT dose level was reduced to 300 mg/m^2/day. At this dose level a partial tumor response was achieved in 57% of cases.

Overall response rates in these three preoperative chemoradiation trials achieved 50–69% and are more favorable in such series treating primary disease than in those with recurrent rectal carcinoma, which was the case in our study.

The main side effects of UFT + LV are gastrointestinal reactions and myelosuppression.[6,18] In our trial DLT was diarrhea and emesis using the MTD of 400 mg/m^2/day UFT and a fixed dose of 90 mg LV concurrently with radiation therapy of the pelvis. As described previously, toxicity due to UFT + LV plus irradiation is similar to that observed in current chemotherapy regimens for rectal carcinoma patients.[5,6,19] The doses of UFT applied in combined radio-chemotherapy schedules are comparable to dose levels recommended for treatments with chemotherapy alone.[6]

As described in our study, UFT + LV simultaneously applied to irradiation did not enhance cutaneous side effects of radiation therapy. This combination regimen is considered to be feasible, especially on an outpatient base.

While UFT + LV treatment alone, if given on a certain schedule day 1–28, may cause moderate myelotoxicity, we did not observe any hematologic toxicity in our trial. This favorable toxicity profile may be ascribed to the interruption of chemotherapy on day 6 and 7 of any treatment week.

Based on the feasibility and side effects reported, the dosage of UFT should be set according to body surface area at 350 mg/m^2/day.

To evaluate feasibility and toxicity of UFT + LV in the adjuvant setting a phase I dose-escalating trial of postoperative UFT + LV plus radiation in rectal cancer is currently open to accrual at the Memorial Sloan-Kettering Cancer Center.[9,18,20,21] The phase I results of clinical and preclinical studies of combined chemoradiation in further tumor entities such as head and neck cancer[22] suggest that the activity of UFT is similar to that described in studies with 5-FU i.v. and justify further evaluation.

Conclusion

Combined chemoradiation with oral UFT + LV is feasible and well tolerated for recurrent rectal cancer patients undergoing pelvic radiation. The safety profile appears comparable to that of i.v. dosing without requiring i.v. port systems.

The recommended doses for further phase II chemoradiation trials in rectal cancer are 350 mg/m^2/day UFT + 90 mg LV.

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