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ORIGINAL ARTICLE

High-dose radiotherapy and concurrent UFT plus l-leucovorin in locally advanced rectal cancer: A phase I trial

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Abstract
A phase I trial of preoperative high dose pelvic radiotherapy and oral UFT/l-leucovorin in patients with locally advanced and unresectable rectal cancer patients to evaluate toxicity and efficacy was performed. Eighteen patients (14 with primary unresectable tumours and four with locally recurrent tumours) were treated. All patients were evaluable for acute toxicity and efficacy. Patients received increasing doses of UFT (150 to 300 mg/m^2/day UFT and a fixed dose of 22.5 mg/day l-leucovorin) with each fraction, five days a week for 30 days, concomitantly with pelvic radiotherapy (60 Gy in 30 fractions using concomitant boost technique). All patients received the planned dose of radiotherapy. No hematological toxicity was observed. Only one patient developed grade 3 toxicity (diarrhea). Fourteen patients (78%) had surgery (11 R0 and 3 R1) after median 40 days. Two patients (11%) had a complete pathological response. Ten patients are alive after median follow-up of 49 months. Toxicity, resection rate and survival are very encouraging and the study continues as a phase II trial.

Introduction

In patients with resectable rectal cancer, preoperative therapy is used to reduce the incidence of local failure and to improve survival [1,2]. In patients with non-resectable tumour preoperative, therapy is needed to allow a subsequent resection with tumour free surgical margins [2–4].

Approximately 10% of patients with rectal cancer present with a locally advanced non-resectable tumour but without distant metastases at the time of diagnosis. Patients with non-resectable local recurrence face the same problems and the two categories (LARC) often receive the same treatment. The prognosis is poor with a median survival of nine–18 months [5,6]. Uncontrolled LARC is associated with substantial morbidity, primarily pain, and in the past palliative radiation was often the only therapy offered [7].

Radiotherapy in a dose of 40–50 Gy in 25 fractions can render a certain fraction of LARC resectable [3,8], and perhaps a higher dose would improve the local control [8–10], although a clear dose-effect relationship has not been proven in radiation treatment of LARC. A higher dose without doubt increases the risk of toxicity, but the higher risk of toxicity may be reduced by modern treatment planning and a technique applying a high dose to the tumour volume only. The concomitant boost technique seems to present an advantage as indicated by radical radiation treatment of both head and neck and cervix cancer [11].

Concomitant chemotherapy and radiation probably improves the effect and increases the chance of complete pathological remission [3,12]. In recent years, a number of phase I and II trials have indicated that resection is possible in more than 50% of the patients receiving combined treatment, and approximately 10% will have complete pathological remission [13]. The chemotherapy has been based on 5-fluorouracil (5-FU) as the drug of choice. There are indications that continuous infusion is more effective than bolus 5-FU [14], but continuous infusion is complicated by the use of central venous catheter and portable infusion pumps causing problems such as venous thrombosis and infection. However, similar serum and tumour concentrations of 5-FU can be obtained by oral therapy [13,15].

UFT (Bristol Myers-Squibb) is an oral formulation of the prodrug tegafur and uracil, which inhibits

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the degradation of 5-FU. The serum concentration of 5-FU on UFT treatment mimics that of continuous infusion of 5-FU. In advanced colorectal cancer, the effect of UFT equals that of 5-FU as shown in two large randomized trials [16,17]. Furthermore, the possibility of the oral administration makes UFT an interesting drug for therapy of rectal carcinoma in combination with radiation therapy, and preliminary results have indicated that adequate serum and intratumoural 5-FU concentration is maintained with a five days a week schedule [18].

The purpose of the present study was to investigate the feasibility of high dose radiotherapy (60 Gy in 30 fractions) in combination with UFT in patients with LARC in a phase I trial. The primary end-point was to assess acute toxicity but as a secondary aim we also wanted to assess efficacy.

Material and methods

Criteria of eligibility

All patients had locally advanced (primary or recurrent) rectal adenocarcinoma (LARC). Patients were eligible if the tumour was fixed to the pelvic wall and unresectable as judged clinically by a colorectal surgeon. MR-scan was not part of the routine investigations. Patients were required to have a WHO performance status 0–2, age 18–80 years, adequate bone marrow, renal and hepatic function (WBC $>3\times10^9$/l, platelet count $>100\times10^9$/l, total bilirubin level $<1.5\times$ upper normal value and creatinine <150 mol/l).

The exclusion criteria were extrapelvic disease, prior systemic chemotherapy or pelvic radiotherapy. In addition, patients who had other prior or concomitant malignant disease were excluded with the exception of adequately treated in situ carcinoma of the uterine cervix and basal or squamous cell carcinoma of the skin.

Trial design

Phase I/II trial with escalating doses of oral UFT (and l-leucovorin) in combination with a fixed high dose of radiotherapy (60 Gy in 30 fractions).

Investigations and follow-up

The pretreatment investigations included a complete history, blood chemistry, physical examination, chest x-ray, and CT-scans or ultrasound scans of the liver were performed.

Overall survival time was calculated as the time from start of therapy until death from any reason or the last date of follow-up.

Ethics

The protocol and the procedures followed were according to the Helsinki Declaration and were approved by the regional and national Ethical Committee.

Radiotherapy

RT was delivered five days per week, once per day, to a total dose of 60 Gy in 30 fractions to the primary tumour. This was accomplished using 27 fractions of 1.8 Gy to the pelvis with a concomitant boost of 27 fractions of 0.2 Gy to the primary tumour, and a final boost of three fractions of 2.0 Gy.

Macroscopically identified tumour tissue (GTV) included the primary tumour and other macroscopically identified tumour. GTV was defined by integrated information obtained by CT- and MR-scan and/or any clinical information. The clinical target volume (CTV) was defined as GTV plus tissue volumes harbouring potential microscopic disease including presacral and perirectal areas with lymph nodes as well as internal iliac lymph nodes.

The upper border of the radiation portals was the junction L5-S1 and the lower border was 3 cm below the primary tumour or 1 cm below the obturator foramen, whichever was more inferior. If there was distal extension of the tumour to the anal verge, the perineum was included.

RT was given by a high-energy megavoltage linear accelerator and patients were treated in the supine position. A 3-beam technique with concomitant boost was used. A posterior (field 1) and two lateral fields (fields 2 and 3) encompassed CTV (1.8 Gy/day) and, as concomitant boost, two lateral boost portals (fields 4 and 5) encompassed GTV with a 1-cm margin (0.2 Gy/day). The two lateral boost portals were also used for a final 6 Gy boost (2.0 Gy/day). CTV thus received 48.6 Gy in 27 fractions and GTV received 60 Gy in 30 fractions. The prescribed dose to GTV was specified according to ICRU 50 and 62 with the isodose distribution to the GTV of at least 95%. All five fields were treated in the same session.

Chemotherapy

Concurrent with radiation cohorts of three patients received increasing doses of oral UFT (150 to 300 mg/m^2/day, five days a week for 30 days), divided in three doses plus a fixed dose of Isovorin 7.5 mg [19,20] with each UFT dose (Table I). Sufficient serum and tumour concentrations can be obtained by this schedule [18]. The dose of UFT was increased if no severe (grade 3 or 4) toxicity was observed. However, the dose was not increased

Table I. UFT dose escalation levels and number of patients.

	UFT mg/m^2	No
Level 0	150	3
Level 1	200	3
Level 2	250	3
Level 3	300	9

beyond 300 mg/m^2/day, which is the recommended standard dose for systemic therapy. At 300 mg/m^2/day, nine patients were included to secure the observed low toxicity.

Toxicity

Toxicity was graded according to NCI Common Toxicity Criteria. Dose limiting toxicity (DLT) was reached if grade 3 toxicity was observed. Cohorts of at least three patients were entered at each dose level and we evaluated each cohort for the entire combined treatment course before dose escalation was allowed. If one or more patients at a given dose level developed DLT, three additional patients were planned to be treated at that dose level. Blood samples were taken every week during chemoradiation.

Antiemetic or antidiarrheal drugs were not offered prophylactically but could be used on demand.

Surgery

The tumour response and resectability was evaluated with an abdominal CT scan and digital rectal examination by an experienced rectal surgeon four weeks after completing the treatment. Surgical resection was planned six weeks after the completion of the chemoradiotherapy.

Statistical evaluation

Non-parametric statistics were applied. All median values are followed by range in brackets. Overall survival curve were generated according to the Kaplan-Meier method.

Results

From May 1998 to September 1999, 18 patients (11 men and 7 women) were treated according to this phase I study. Median age was 65 years (range 31–74 years) and all patients had performance status 0 or 1. Fourteen patients had primary LARC and four patients had recurrent pelvic disease. Median tumour size was 7 cm (range 4–10 cm).

All 18 patients received the planned preoperative 60 Gy in 30 fractions. Median duration of RT was 43 days (range 39–48 days). Seventeen patients received the planned dose of UFT (three patients received 150, 200, and 250 mg/m^2, respectively and nine patients received 300 mg/m^2, Table I). One patient discontinued UFT (300 mg/m^2) by own request (nausea grade 1) after one week, but continued and completed RT. Table II shows acute toxicity associated with preoperative chemoradiation. No hematological toxicity was observed. Non-hematological toxicity grade 1 or 2 (diarrhea, nausea, or dysuria) was seen in most patients. Only one case of grade 3 toxicity was observed, a patient receiving UFT 300 mg/m^2/day developed grade 3 diarrhea, which responded well to antidiarrheal drugs (Table II).

Two patients had clinical complete response, eight patients had partial response, eight patients had stable disease as evaluated by clinical examination and CT scan. One patient developed extrapelvic metastatic disease. Fourteen patients (78%) went on to have surgical resection (11 R0 and 3 R1) after median 40 days (range 22–82 days). Two patients (11%) with a clinical CR and PR respectively had a complete pathological response (pCR). Three patients still had clinical non-resectable disease and one patient had progressive disease outside the radiation field and a laparotomy was not performed. Postoperative therapy was not part of this protocol but four to six months of adjuvant systemic therapy was offered to five out of 12 patients with lymph node metastases.

Survival is very encouraging (Figure 1). Eight patients died after median 12 months (range 11–27 months) but ten patients are alive after a median follow-up of 49 months (range 46–62 months).

Discussion

There is no agreed definition of LARC [4,8] but patients were included in the present study if the tumour was fixed and unresectable as judged clinically by an experienced colorectal surgeon. In these patients, primary radical resection is seldom possible but it is now clear that a combination of radiotherapy and chemotherapy can produce tumour shrinkage which allows radical surgery in more than 50% of the

Table II. Toxicity according to CTC.

	Grade 1%	Grade 2%	Grade 3%
Leucopenia	0	0	0
Trombopenia	0	0	0
Nausea/vomiting	29	7	0
Diarrhea	36	43	7
Skin	29	14	0
Dysuria	22	7	0
Pain	36	14	0

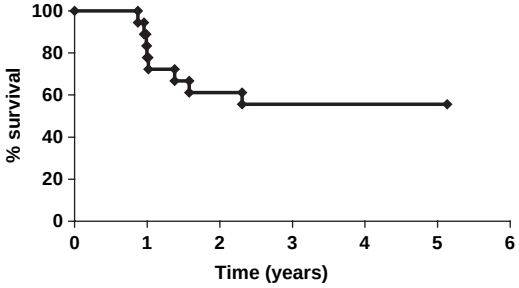

Figure 1. Kaplan-Meier estimation of overall survival in 18 patients with LARC pretreated with chemoradiation (60 Gy and UFT) before surgery (in 14 patients).

patients [8]. It may be anticipated that the improved tumour remission translates to survival benefit although this has not been proven in randomized trials.

The present study presents high dose radiation and concurrent chemotherapy. The rate of acute complications, however, was very low. Only one patient had grade 3 toxicity and only one patient did not receive the planned dose of UFT (the patient stopped UFT after one week of therapy due to nausea). All 18 patients received the planned 60 Gy protocol dose without any delay (median duration of radiotherapy was 43 days). Furthermore, the treatment did not seem to increase the operative risk. None of the 18 patients presented with a serious complication requiring re-operation and no fatality within 30 days was recorded. One explanation may be that the radiation technique with five fields implies that only a small volume receives the high dose. Compared to conventional three fields therapy (one posterior and two lateral fields), the technique used in the present study allows a substantial sparing of both bladder and intestines. The dose outside GTV with a small margin was only 48.6 Gy. Thus, concomitant boost technique presents an easy way to differentiate the dose level between tumour and lymph node at risk.

Preoperative RT (with or without chemotherapy) is more effective than postoperative therapy in patients with resectable rectal cancer [1,2]. Several studies over the past decade have reported that a combination of RT and 5-FU, bolus or CVI, and with or without leucovorin (LV) can induce pathologic complete response (pCR) in 10 to 20%, depending on efficacy and selection of patients [3]. Continuous venous infusion of 5-FU (CVI) is the standard regimen in conjunction with radiotherapy in postoperative chemoradiotherapy [14], but the substitution of oral therapy (UFT/Lv or Capecitabine) for CVI is more convenient for patients and probably as effective [13,21]. No study has compared efficacy and toxicity of UFT and capecitabine in combination with radiotherapy but hand-foot syndrome I seen more often in patients receiving capecitabine [8].

The combination of UFT (with or without LV) with RT has been reported in number of phase I and II studies primarily in primarily cancer of the rectum [22–27] but also in a range of other gastro-intestinal malignancies [8,28]. In most studies 45 Gy to 50 Gy was used and none have used UFT and leucovorin (Lv) in combination with a radiation dose of 60 Gy in 30 fractions. Diarrhea grade III-IV was seen in up to 40% of patients and was in all cases the dose-limiting toxicity [22–27].

The recommended dose of UFT in most studies was 300 mg/m^2 (with a range from 260 to 350 mg/m^2) given five days a week.

The optimal dose of leucovorin is not known and there is no evidence that a higher dose (e.g. 90 mg daily) has a better effect than 45 mg daily (equilvalent to pure l-leucovorin in a dose of 22.5). In combination with radiotherapy and UFT the dose has ranged from 0 to 90 mg/day [22–27].

Hoff et al. [22] presented a phase I trial including 15 patients with stage 2 or 3 rectal cancer receiving preoperative radiation (45 Gy). During delivery of radiation therapy, patients received increasing doses of UFT and a fixed dose of Lv (90 mg/d) daily for the five consecutive days of radiation each of the five weeks of radiation treatment. They concluded that MTD of UFT was 350 gm/m^2/day, and suggested a dose of 300 mg/m^2 for further studies as also used in the present study. Three patients had pCR.

De la Torre et al. [23] have reported a phase II trial of UFT and Lv administered concomitantly with pelvic radiotherapy (45 Gy) in patients with LARC but they used a different schedule. Patients received UFT 300 mg/m^2/day and Lv 30 mg/day on days 8–35 concomitantly with radiotherapy and three patients obtained pCR. Eight of 35 (23%) patients developed grade 3 diarrhea.

A phase II study performed by Feliu et al. [24] also examined preoperative therapy with UFT and Lv in combination with radiotherapy (45 GY plus boost 5.4 Gy) in 41 patients with resectable T3 or T4 rectal cancer but they also used a different schedule. Patients received UFT (300 or 350 mg/m^2/day) twice daily on days 1–14, Lv 500 mg/m^2 intravenously on day 1, and 15 mg Lv orally twice daily on days 2–14 every four weeks. More than 50% of patients were downstaged and three patients obtained pCR (11%). Nine patients (32%) experienced grade 3 or 4 toxicity consisting of diarrhea, vomiting or mucositis (7/16 of patients who received 350 mg/m^2 of UFT). The occurrence of unacceptable toxicity resulted in a reduction in the UFT starting dose to 300 mg/m^2/day. Only two of the remaining 12 patients (16%) developed grade 3

diarrhea. They concluded that longer follow-up is needed to determine whether this strategy will ultimately improve local control or survival.

Fernandez-Martos et al. [25] used a combination of radiotherapy (45 Gy in 25 fractions) and UFT (400 mg/m^2/d, five days a week without leukovorin) in 94 patients with resectable rectal cancer. All patients received the full radiation dose but 15 patients needed dose reduction of UFT. Diarrhea grade III was seen in 14%. Resection was performed in 91 patients, 9% had pCR and further 23% had only residual microscopic foci left. At three years OS was 75%.

Even though we present data from a phase I study, long-term results with ten out of 18 patients alive after a median follow-up of 49 months are very encouraging and therefore this phase I study has continued as a phase II study to determine the number of patients achieving radical surgery (R0) but acute and late toxicity will also be evaluated.

Preoperative high-dose RT (60 Gy in 30 fractions using concomitant boost technique) and concurrent oral UFT/Isovorin to patients with LARC can be delivered with low toxicity. The combination downstages most patients with LARC, pathologically complete responses are seen and survival are very promising.

References

[1] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal Cancer. NEJM 2004;351:1731–40.

[2] Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol 2003;42:476–92.

[3] Glimelius B. Chemoradiotherapy for rectal cancer-is there an optimal combination? Ann Oncol 2001;12:1039–45.

[4] Sebag-Montefiore D. Treatment of T4 tumours: the role of radiotherapy. Colorectal Dis 2003;5:432–5.

[5] Gunderson LL. Indications for and results of combined modality treatment of colorectal cancer. Acta Oncol 1999; 38:7–21.

[6] Overgaard M, Bertelsen K, Dalmark M, et al. A randomized feasibility study evaluating the effect of radiotherapy alone or combined with 5-fluorouracil in the treatment of locally recurrent or inoperable colorectal carcinoma. Acta Oncol 1993;32:547–53.

[7] Frykholm GJ, Pahlman L, Glimelius B. Treatment of local recurrences of rectal carcinoma. Radiother Oncol 1995;34: 185–94.

[8] Reerink O, Mulder NH, Szabo BG, et al. Developments in treatment of primary irresectable rectal cancer. Colorectal Disease 2004;6:406–17.

[9] Mohiuddin M, Regine WF, John WJ, et al. Preoperative chemoradiation in fixed distal rectal cancer: Dose time factors for pathological complete response. Int J Radiat Oncol Biol Phys 2000;46:883–8.

[10] Glimelius B, Isacsson U, Jung B, Påhlman L. Radiotherapy in addition to radical surgery in rectal cancer: Evidence for a dose response effect favouring preoperative treatment. Int J Radiat Oncol Biol Phys 1997;37:281–7.

[11] Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7–16.

[12] Frykholm GJ, Påhlman L, Glimelius B. Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiation Oncology Biol Phys 2001;50:427–34.

[13] Minsky BD. UFT Plus Oral Leucovorin Calcium [Orzel™] and Radiation in Combined Modality Therapy: A Comprehensive Review. Int J Cancer [Radiat Oncol Invest] 2001;96: 1–10.

[14] O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994;331:502–7.

[15] Saad ED, Hoff PM. UFT and Oral Leucovorin as Radiation Sensitizers in Rectal and Other Gastrointestinal Malignancies. Cancer Investigation 2003;21:624–9.

[16] Carmichael J, Popiela T, Radstone D, et al. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3617–27.

[17] Douillard JY, Hoff PM, Skillings JR, et al. Multicenter Phase III Study of Uracil/Tegafur and Oral Leucovorin Versus Fluorouracil and Leucovorin in Patients With Previously Untreated Metastatic Colorectal Cancer. J Clin Oncol 2002;20:3605–16.

[18] Sadahiro S, Suzuki T, Kameya T, et al. A pharmacological study of the weekday-on/weekend-off oral UFT schedule in colorectal cancer patients. Cancer Chemother Pharmacol 2001;47:447–50.

[19] Gyldenkerne N, Glimelius B, Frödin JE, et al. A phase II study of UFT and leucovorin in combination with Mitomycin C in patients with metastatic colorectal cancer. Acta Oncol 2004;43:276–9.

[20] Jakobsen A, Pfeiffer P, Hansen F, Sandberg E, Aabo K. Dual modulation of UFT with leucovorin and hydroxyurea in metastatic colorectal cancer. Acta Oncol 2001;40: 63–6.

[21] Crane CH, Sargent DJ. Substitution of oral fluoropyrimidines for infusional fluorouracil with radiotherapy: how much data do we need? J Clin Oncol 2004;22:2978–81.

[22] Hoff PM, Janjan N, Saad Ed, et al. Phase I study of preoperative oral uracil and tegafur plus leucovorin and radiation therapy in rectal cancer. J Clin Oncol 2000;18: 3529–34.

[23] De la Torre A, Ramos S, Valcarcel FJ, et al. Phase II study of radiochemotherapy with UFT and low-dose oral leucovorin in patients with unresectable rectal cancer. Int J Radiat Oncol Biol Phys 1999;45:629–34.

[24] Feliu J, Calvillo J, Escribano A, et al. Neoadjuvant therapy of rectal carcinoma with UFT-leucovorin plus radiotherapy. Ann Oncol 2002;13:730–6.

[25] Fernandez-Martos C, Aparicio J, Bosch C, et al. Preoperative uracil, Tegafur, and concomitant radiotherapy in operable rectal cancer: a phase II multicenter study with 3 years' follow-up. J Clin Oncol 2004;22:3016–22.

[26] Pfeffer MR, Kundel Y, Zehavi M, et al. A phase I study of oral UFT given concomitantly with standard preoperative radiotherapy for rectal cancer. IMAJ 2004;6:595–8.

[27] Schiebe ME, Reese T, Wenz F, et al. Phase I study of oral uracil and Tegafur plus leucovorin and pelvic radiation in patients with recurrent rectal cancer. Anti-cancer drugs 2002;13:1005–9.

[28] Bystrom P, Frodin JE, Berglund A, Wilking N, Glimelius B. Phase I study of UFT plus leucovorin with radiotherapy in patients with inextirpable non-rectal gastrointestinal cancer. Radiother Oncol 2004;70:171–5.