original article

Annals of Oncology 17: 246–251, 2006
doi:10.1093/annonc/mdj041
Published online 9 November 2005

Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study

A. De Paoli[1]*, S. Chiara[2], G. Luppi[3], M. L. Friso[4], G. D. Beretta[5], S. Del Prete[6], L. Pasetto[4], M. Santantonio[3], E. Sarti[5], G. Mantello[6], R. Innocente[1], S. Frustaci[1], R. Corvò[2] & R. Rosso[2]

[1]Departments of Radiation Oncology and Medical Oncology, C.R.O. – National Cancer Institute, Aviano; [2]Departments of Radiation Oncology and Medical Oncology, I.S.T. – National Institute of Cancer Research, Genova; [3]Departments of Radiation Oncology and Medical Oncology, University Hospital, Modena; [4]Departments of Radiation Oncology and Medical Oncology, University Hospital, Padova; [5]Departments of Radiation Oncology and Medical Oncology, Ospedali Riuniti, Bergamo; [6]Departments of Radiation Oncology and Medical Oncology, General Hospital, Ancona, Italy

Received 28 June 2005; revised 9 September 2005; accepted 12 September 2005

Background: The aim of the study was to evaluate tolerance and efficacy of preoperative treatment with capecitabine in combination with radiation therapy (RT) in patients with locally advanced, resectable, rectal cancer.
Patients and methods: Fifty-three patients with potentially resectable T3, N0–2 (87%) and T4, N0–2 (13%) rectal cancer were treated with capecitabine (825 mg/m^2, twice daily for 7 days/week) and concomitant RT (50.4 Gy/28 fractions). Patients underwent surgery after 6–8 weeks followed, upon physician's indications, by 4-months adjuvant capecitabine. The primary end point was to determine the rate of pathologic complete response. Secondary end points were to assess the rate of clinical response and the safety profile.
Results: All patients but two completed the RT programme and 47 (89%) received 81%–100% of the capecitabine dose (100% of dose in 72% patients, 81%–95% in 17% patients and 48%–74% in 11% of patients). No patient had grade 4 toxicity. Grade 3 toxicity occurred in six patients (11%) and consisted mainly of leucopenia (4%) and hand–foot syndrome (4%). Mild or moderate toxicity was common and included leucopenia (72%), diarrhea (40%), proctitis (34%) and skin toxicity (20%). The overall clinical response rate was 58% and the downstaging rate was 57%, with a pathologic complete response rate of 24%. Among 34 patients with low-lying tumors (≤5 cm from anal verge), 20 (59%) had a sphincter-saving operation.
Conclusions: Preoperative chemoradiation with capecitabine and RT appeared to be effective in locally advanced resectable, rectal cancer. The favorable safety profile of the combination might warrant the use of capecitabine and RT with other effective new drugs.
Key words: capecitabine, chemoradiation, locally advanced rectal cancer, phase II study

introduction

Preoperative radiation therapy (RT) with concurrent 5-fluorouracil (5-FU)-based chemotherapy (CT) has received an increasing interest over the last decade in the treatment of resectable, stage II–III, rectal cancer. Although large randomized trials have shown that preoperative RT alone, given with short-course fractionation followed by immediate surgery, can significantly increase local control [1, 2] and survival [1] compared with surgery alone, combined CT–RT has received an increasing interest because of the possibility that it may also promote a sphincter-preservation procedure [3].

On the basis of the favorable results of postoperative RT combined with 5-FU-based chemotherapy [4–7], patients with clinical T3 and/or positive lymph nodes have been treated in many phase II studies with preoperative RT and concurrent bolus 5-FU/leucovorin or continuous infusion (ci) 5-FU followed by surgery and, generally, postoperative 5-FU-based CT. In these studies, pathologic complete response (pCR) rates ranged from 9% to 29%, the incidence of grade 3–4 acute toxicity ranged from 15% to 25% and local recurrence rates ranged from 3% to 17% [3]. In addition, a sphincter-preservation procedure was reported in up to 75% of patients who, at presentation, were considered to need an abdominal–perineal resection. These indications have been confirmed by the results recently reported in randomized trials, which have demonstrated a significant increase in pathological response rate with the addition of CT to preoperative RT compared with

Correspondence to: Dr A. De Paoli, Department of Radiation Oncology, C.R.O. – National Cancer Institute, Aviano, Italy. Tel: +39-0434-659-528; Fax: +39-0434-659-524; E-mail: adepaoli@cro.it

preoperative RT alone [8], as well as a significant improvement in local control and sphincter-preservation rates with preoperative compared with postoperative CT–RT [9].

The concurrent ci-5-FU administration with RT offers the biological advantage of achieving a prolonged exposure of tumor cells to effective levels of 5-FU, thereby improving 5-FU radiosensitization activity [10, 11]. Despite the lack of studies comparing bolus versus ci-5-FU in combination with preoperative RT, the available data on 5-FU efficacy and toxicity, from selected preoperative series [12, 13], and from randomized trials in the postoperative setting [7, 14] seem to be in favor of ci-5-FU administration. However, the need of long-term venous access for portable pumps may limit the use of ci-5-FU therapeutic regimens.

Capecitabine is an oral fluoropyrimidine carbamate, which is converted to 5-FU preferentially in tumor cells through exploitation of higher activity of the enzyme thymidine phosphorylase (TP) in tumor tissue compared with normal tissue [15]. The tumor-preferential activation of capecitabine reduces systemic exposure to 5-FU and potentially improves efficacy and safety [16]. As an oral agent, capecitabine could achieve a continuous exposure to 5-FU in a manner similar to infusional regimens [17], but avoiding the risk of central venous access complications. In addition, preclinical studies have shown that RT can up-regulate the TP expression in tumor cells, resulting in a selective synergistic effect between RT and capecitabine [18]. Therefore, capecitabine offers an interesting alternative to ci-5-FU, especially in combination with RT.

A phase I study in rectal cancer defined the recommended dose of capecitabine to be 825 mg/m^2 b.i.d., administered 7 days/week during a conventional RT period of about 6 weeks. The dose-limiting toxicity was defined by the hand–foot syndrome, occurring at a capecitabine dose of 1000 mg/m^2 b.i.d. Other toxicities were generally mild to moderate [19]. This study demonstrated that capecitabine could be combined with RT at an overall dose similar to that used when capecitabine is employed as a single agent for metastatic disease either in the 42-day continuous regimen (829 mg/m^2 b.i.d.) or in the intermittent schedule (1250 mg/m^2 b.i.d. for 2 weeks, every 3 weeks) [20, 21].

Based on these considerations, we carried out a multicentre phase II study to evaluate the efficacy and safety of capecitabine combined with preoperative RT in locally advanced, resectable, rectal cancer. The primary end point was to determine the pCR rate and secondary end points were to assess clinical response rate and safety profile.

patients and methods

This study was performed according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The study was approved by the ethics committee of the six participating centers and each patient signed an informed consent before inclusion in the study.

eligibility criteria

Patients with histologically confirmed diagnosis of locally advanced, resectable, clinical stage T3 or T4, N0 or N1–2, M0, suitable for preoperative combined radiochemotherapy, were eligible for the study. All patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, age between 18 and 80 years and adequate hematological, liver and renal function.

Exclusion criteria included previous RT on the pelvic region or previous CT; patients with serious illness or medical conditions including significant cardiac disease, history of significant neurological or psychiatric disorders, serious uncontrolled active infection; pregnant or lactating women and women with child-bearing potential unless using a reliable contraceptive method; sexually active males unwilling to practice contraception during the study; patients with history of previous malignancy except cured non-melanoma skin cancer and *in situ* cervical carcinoma; patients with absolute neutrophil count $<2 \times 10^{-9}$/l or platelet count $<100 \times 10^{-9}$/l, total bilirubin >1.5 times the upper normal limits (UNL) of the institutional normal values, transaminase or alkaline phosphatase >1.5 times UNL and creatinine >1.6 mg/dl.

pretreatment evaluation

Baseline assessment included complete history and physical examination, colonoscopy and rigid rectoscopy, pelvic and abdominal computed tomography, endorectal ultrasound (if clinically feasible) and/or pelvic magnetic resonance imaging (MRI), chest X-ray, ECG and hematology and blood chemistry including carcinoembryonic antigen level.

chemotherapy

Capecitabine was administered orally at a dose of 825 mg/m^2 twice a day throughout the RT course. The first daily dose was administered approximately 2 h before RT with the second dose taken 12 h after. Since capecitabine was supplied in 150 and 500 mg tablets, the total daily dose, calculated in terms of mg/m^2, was rounded to the nearest combination of 150 and 500 mg tablets, with the result that two equally divided doses were given.

radiation therapy

A radiation dose of 45 Gy was given to the posterior part of the pelvis to include the tumor, the mesorectum, the posterior walls of the bladder and prostate/vagina, and the internal iliac nodes (clinical target volume 1 or CTV1) followed by a boost of 5.4 Gy limited to the tumor and corresponding mesorectum with a 2 cm margin (clinical target volume 2, CTV2) for a total dose of 50.4 Gy. For T4 tumors, external iliac nodes were also included in CTV1. A conventional fractionation of 1.8 Gy/day, 5 days a week, was used for an overall planned treatment time of 5.5 weeks. Patients were treated in the prone position using a dedicated device to minimize exposure of the small bowel. A three- or four-shaped field box-technique with high-energy photons (≥6 MV) was used. A computed tomography-based treatment planning system was mandatory to define the planning target volume (CTV + 1 cm margin).

surgery

Surgery was planned 6–8 weeks after the completion of radiochemotherapy. Total mesorectal excision (TME) was advisable, while the decisions regarding which form of surgery (abdominal–perineal resection or low-anterior resection) and whether a temporary colostomy should be performed were left to the surgeon's discretion.

toxicity assessment and dose modifications

Toxicity was evaluated weekly in each patient with physical examination, complete blood count with differential and blood chemistry. The intensity of clinical adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0) [22].

The following recommendations for dose reduction were used: if a patient experienced grade 2 or 3 toxicity considered mainly related to capecitabine, drug administration was interrupted until toxicity resolved to grade 0–1,

and then restarted at 75% of the original dose. If a grade 2 or greater toxicity recurred, capecitabine was discontinued again until toxicity resolved to grade 0–1 and then restarted at 50% of the original dose. The RT programme was not altered unless the severity of toxicity worsened; in that case, RT was also discontinued until toxicity recovery.

If a toxicity was considered mainly related to RT and occurred at grade 2 or greater, RT was discontinued until toxicity resolved to grade 0–1 and then restarted. Capecitabine administration was not altered unless the toxicity worsened, in which case capecitabine was also discontinued. If any grade 4 toxicity developed, combined treatment was discontinued.

definition of response

Analysis of response was defined both clinically and pathologically. Clinical response was evaluated according to WHO criteria using the same diagnostic tool employed prior to RT–CT [23]. A tumor and/or nodal downstaging was considered when pathologic T (pT) and/or pathological N (pN) was lower than clinical T and/or N as defined by endorectal ultrasound, computed tomography or MRI. Pathologic response was defined according to the pTNM staging system, version 5 [24]. Serial sectioning of the specimen was performed and tumor area, with or without macroscopic residual tumor, was entirely sampled for histological examination. A pCR was considered when no malignant cells were observed in the surgical specimen.

postoperative treatment

Following surgery, four cycles of capecitabine were given to patients who were considered by the treating physician to potentially benefit from postoperative therapy. Capecitabine was administered at a dose of 1250 mg/m^2 twice daily on days 1–14, every 3 weeks.

statistical methods

The aim of this study was to determine the pCR rate. Simon's method was used to calculate the sample size. Considering the optimal two-stage design for a phase II study, with the difference p1–p0 = 15% between 'standard' chemoradiation with ci-5-FU or 5-FU/leucovorin (p0 = 10) and 'new therapy' (p1 = 25%), and fixing error probabilities (a = 0.05 and B = 0.20), the number of patients for the first step was 18. If two or less pCRs were seen in these 18 patients, the study had to be terminated; otherwise, the accrual had to be continued to a total of 43 patients. As there were more than two responding patients (pCR) at the interim analysis for the first step, the study proceeded to the second step and an additional 25 patients were accrued. After a total of 43 patients, the accrual continued assuming that about 10% or more patients could be not evaluable. A total of 53 patients were enrolled.

results

A total of 53 patients were recruited to the study between September 2001 and July 2003. Their clinical and demographic characteristics are shown in Table 1. The median age was 63 years (range 29–80) and the majority of patients (87%) had T3, N0–2, M0 stage of disease. The median distance from the lower pole of the primary tumor to the anal verge was 4 cm (range 2–10) and 36 patients (68%) had tumors between 2 and 5 cm from this reference point. All 53 patients were evaluable for clinical response and safety to treatment, whereas 51 patients were evaluable for pathologic response and downstaging.

toxicity and compliance to treatment

Overall, preoperative capecitabine and RT were well tolerated and the most commonly reported events are shown in Table 2.

Table 1. Patient characteristics

	No. of patients (N = 53)	%
Age (years)		
Median	63	
Range	29–80	
Gender		
Male	39	74
Female	14	26
ECOG performance status		
0	49	92
1	4	8
TNM clinical stage		
T3 N0	21	40
T3 N1–2	25	47
T4 N0	1	2
T4 N1–2	6	11

Table 2. Acute toxicity

Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)
Hematological			
Anemia	11 (21)	6 (11)	2 (4)
Leucopenia	22 (42)	14 (26)	2 (4)
Thrombocytopenia	15 (28)	–	1 (2)
Non-hematological			
Diarrhea	13 (24)	8 (16)	1 (2)
Proctitis	11 (21)	7 (13)	–
Cystitis	7 (13)	3 (4)	1 (2)
Skin	6 (11)	5 (9)	2 (4)
Hand–foot	3 (5)	3 (4)	2 (4)

Neither grade 4 toxicity nor treatment-related deaths were reported.

Non-hematological toxicity of grade 1 or 2 occurred in about half of the patients and consisted mainly of diarrhea (40%) and proctitis (34%). However, grade 2 diarrhea and/or proctitis, which generally ameliorated with medications, were the reason for capecitabine interruption and dose modification in four patients only, whereas none of the patients with grade 1 and 2 toxicity required RT interruption.

Non-hematological toxicity of grade 3 included hand–foot syndrome in 4%, perianal skin toxicity in 4%, cystitis in 2% and diarrhea in 2% of the patients. These toxicities were the reason for capecitabine interruption and dose reduction in an additional four patients; in two of these patients both capecitabine and RT were definitively interrupted after 43.2 Gy and 21.6 Gy, respectively. This last patient, a 79-year-old female who also developed grade 3 leucopenia and thrombocytopenia, did not restart RT and capecitabine after 21.6 Gy after toxicity resolved because of persistent symptomatic disease, which required immediate surgery.

Hematological toxicity was the most common toxicity encountered in this study. However, only the 79-year-old patient developed grade 3 leucopenia and thrombocytopenia and another patient had grade 3 leucopenia alone. Twenty-two

patients (42%) experienced grade 1 and 14 (26%) experienced grade 2 leucopenia. Leucopenia of any grade, either as the only toxicity or as a component of toxicity, was the reason for capecitabine dose reduction in 12 patients.

Generally, leucocyte count showed a decrease within the third week of treatment, but remained quite stable afterwards without any trend towards cumulative toxicity. Platelet count showed a similar decrease during the initial 3 weeks of treatment, but it did not exceed grade 1 thrombocytopenia except for the above mentioned case of grade 3 hematological toxicity. Grade 1 or 2 anemia (41%) was also reported, although it could not be directly related to treatment because of persistent tumor bleeding in some patients.

Overall, 15 patients necessitated capecitabine dose adjustment whereas capecitabine was definitely discontinued in three of them. As a result, of the 53 patients, 38 (72%) had 100%, nine (17%) had 81%–95% and six (11%) had 48%–74% of the planned capecitabine dose. Only two patients required a definitive interruption of RT, whereas in the remaining patients the RT programme was neither modified nor delayed, except for technical reasons, resulting in a RT compliance of 96%.

clinical response

All patients were evaluated for clinical response after completion of RT–CT. Tumor response was assessed unidimensionally (28%) or bidimensionally (72%) by computed tomography or MRI. The overall response rate was 58%: two patients (4%) had a complete response (CR), 29 (54%) had a partial response (PR) and 22 (42%) minor or stable disease (NC). No patient showed disease progression on primary tumor, whereas two patients had liver metastases at preoperative restaging or at operation, with PR on the primary tumor.

surgery

Of the 53 patients treated with preoperative capecitabine and RT, 51 underwent surgical resection, one patient had unresectable disease at operation (he was NC after radiochemotherapy) and another refused surgery. Of the 51 patients treated with surgery, 48 had a radical R0 resection (33 a low-anterior resection, 15 an abdominal–perineal resection) and three had a trans-anal full-thickness local excision. The three patients who had local excision were selected for such a procedure because of major clinical response, low-lying tumor and expected abdominal–perineal resection procedure, which the patients refused. Overall, sphincter-saving surgery was achieved in 36 of 51 patients. In 34 of the operated patients, the distance of the lower pole of the tumor from the anal verge was ≤5 cm and 20 (59 %) of them received a sphincter-saving procedure.

No perioperative deaths were reported. Details of the surgical complications as well as anorectal function in the patients who had a sphincter-saving procedure will be reported in a future paper.

pathologic response and downstaging

Pathologic examination of the surgical specimen of the 51 operated patients showed a pCR rate of 24% (12 of 51 patients). Overall, tumor downstaging was reported in 29 of 51 (57%) patients (Table 3). Nodal downstaging was observed in 22 of 28 (78%) of the operated patients with clinical N1–N2 disease. No evidence of nodal involvement was observed in 38 of 48 patients (79%) who underwent a radical operation.

Table 3. Pathologic tumor response

T Stage	pT0	pT1	pT2	pT3	pT4
T3	12	2	11	20	–
T4	–	–	1	3	2
Total	12	2	12	23	2

discussion

Preoperative combined-modality treatment with ci-5-FU and RT is now a well accepted approach in the management of patients with locally advanced rectal cancer.

The more recent availability of new effective drugs that replicate the antitumor mechanism of 5-FU, including oral fluoropyrimidines such as capecitabine, uracile and tegafur (UFT), and a new generation of thymidylate synthase inhibitors such as raltitrexed, have provided the opportunity to explore new CT–RT combinations in rectal cancer. One of the major advantages of these new CT–RT combinations is the avoidance of central lines. More importantly, capecitabine is converted to 5-FU by the TP enzyme, which is upregulated by radiation, and this mechanism may improve the likelihood of capecitabine-enhanced radiosensitization [15].

A phase I study combining escalating doses of capecitabine with RT, 50.4 Gy with 1.8 Gy daily fractions, as preoperative, postoperative or palliative treatment of patients with rectal cancer, has been reported by Dunst et al. [19]. Capecitabine was increased from 250 to 1250 mg/m^2 b.i.d., 7 days/week. The dose-limiting toxicity was defined by grade 3 hand–foot syndrome at a capecitabine dose of 1000 mg/m^2 b.i.d. Therefore, the recommended dose of capecitabine for further phase II studies was 825 mg/m^2 b.i.d. In a similar phase I study by Ngan et al. [25], capecitabine, given on a 5 days/week schedule (Monday to Friday) in combination with 50.4 Gy of RT, increased from 425 to 1000 mg/m^2 b.i.d. The dose-limiting toxicity was grade 3 skin reaction and grade 3 diarrhoea with dehydration at the capecitabine dose of 1000 mg/m^2 b.i.d. Although with a different toxicity profile, the recommended capecitabine dose of 900 mg/m^2 b.i.d. reported in this study was comparable to the 825 mg/m^2 b.i.d. reported by Dunst's study, which employed a 7 days/week capecitabine schedule.

In the present phase II study, 53 patients with locally advanced, but resectable, rectal cancer were treated with preoperative RT, 50.4 Gy in 28 fractions, combined with capecitabine at the recommended dose of 825 mg/m^2 b.i.d. throughout the RT course. The patients were evaluated for clinical response rate, percentage of downstaging and tolerance to treatment.

Of the 53 patients, 31 (58%) had a clinical response including two complete and 29 partial responses. This data may not be comparable with other experiences, which generally report a 70%–90% clinical response rate [26, 27]. However, evaluation of clinical response still remains a difficult problem in this

tumor site. Some patients in our study had unidimensionally computed tomography or MRI evaluation and, therefore, tumor response could have been underestimated.

The primary end point of the study was to determine the pCR rate. Compared with clinical stage at baseline, tumor downstaging was observed in 29 of 51 evaluable patients (57%), including 12 patients (24%) with pCR. Nodal downstaging was reported in 78% of patients.

The pCR rate of 24% was consistent with that observed in other recently reported phase II studies with capecitabine and RT. Dupuis et al. [28] reported a 24% pCR rate in the GERCOR trial, which included 51 patients with resectable (98% stage T2–3) rectal cancer. The treatment program was similar to our schedule of 45 Gy RT and concurrent capecitabine at a dose of 825 mg/m^2 b.i.d., 7 days/week. Preliminary data by Dunst et al. [29] from their ongoing phase II study have shown a pCR rate of 4% and a downstaging rate of 74% in more locally advanced disease (50% stage T4).

These results compare well with those reported with ci-5-FU [12, 13] and with those recently reported also by randomized trials with bolus 5-FU/LV and RT [3, 8, 30], both reporting a pCR rate ranging from 27% to 29% and from 14% to 17%, respectively. In addition, these results compare well with those observed in other studies with new drug–RT combinations including capecitabine/leucovorin, UFT and raltitrexed.

Kim et al. [31] reported a 63% tumor downstaging and a 31% pCR rate with an intermittent schedule of capecitabine (825 mg/m^2 b.i.d., days 1–14 and 21–35) in combination with leucovorin (20 mg/m^2, days 1–14 and 21–35) for locally advanced, resectable, rectal cancer. More recently, in a study by Fernades-Martos et al. [32] with uracil/tegafur and RT in operable rectal cancer, tumor downstaging was 54% and the level of pCR was 9%. The antitumor activity of this combination was less favorable when compared with our data on capecitabine and RT. A phase II study with preoperative raltitrexed and RT has been reported by Gambacorta et al. [27] in patients with T3 or T2 N1–2, resectable disease. The results were similar to those reported in our study with a 63% tumor dowstaging and a 24% pCR rate, respectively.

The incidence of acute toxicity during capecitabine–RT was very low. As expected, no grade 4 toxicity was reported and grade 3 toxicity was observed in only six patients (11%), including hematological (2%–4%) and non-hematological (2%–4%) toxicity. Similarly, low toxicity rates have been reported in other capecitabine-RT phase II trials [28, 29].

These data compare favorably with those reported with preoperative RT combined with ci or bolus 5-FU; in addition, they appear similar, but with a possible improvement in the safety profile, to those reported with UFT and raltitrexed. The results from published series with preoperative RT and 5-FU-based CT, show a high incidence of grade 3+ toxicity (15%–25%). In studies with uracil/tegafur and RT [32], although with a decreased incidence, grade 3+ diarrhea was reported as the most frequent toxicity (14%) and grade 3 leucopenia was the most frequent severe toxicity (9%) with RT and raltitrexed [27].

In our study, even if mild and moderate toxicity were common, only a total of 15 patients (28%) required capecitabine dose reduction and most of the study patients (89%) were able to receive 81%–100% of the capecitabine planned dose. Moreover, 96% of patients received the full RT course with a total dose of 50.4 Gy. Therefore, these data confirm the feasibility of our treatment programme and the high level of compliance reported in the previous phase I study [19].

All but two patients underwent surgery and most of them (36 of 51) had a conservative operation. In particular, of the 34 patients with low-lying tumors (≤5 cm from anal verge), 20 (59%) had a sphincter-saving procedure. The data on conservative surgery compare fairly well with other studies [3, 9, 13, 26, 27] and, interestingly, they have been obtained by a multicenter study. Although in a randomized trial comparing two different preoperative approaches, sphincter-preservation did not increase significantly in spite of the increased clinical response rate [33], other experiences demonstrated a significant correlation between response to preoperative RT–CT and the possibility of a sphincter-preserving procedure [34].

As response to preoperative CT–RT has been reported to possibly increase the feasibility of a sphincter-preserving surgery and, potentially, to impact on disease control and survival [13, 26, 34] newer strategies in preoperative treatment of rectal cancer have been directed to obtain higher complete response rates. The combination of 5-FU with new effective drugs in colorectal cancer, such as oxaliplatin and irinotecan, has demonstrated a significant increase in responses in advanced disease. Phase I–II studies evaluating the combination of RT with 5-FU and oxaliplatin or irinotecan are currently ongoing and preliminary results are becoming available [35–37]. Capecitabine, an active and safe oral fluoropyrimidine in combination with RT as demonstrated by our study, might simplify chemoradiation by replacing ci-5-FU and the necessity of central lines in these newer preoperative approaches. Initial experiences with phase I–II studies combining preoperative RT and capecitabine with oxaliplatin [38] or irinotecan [39] seem encouraging and are, at the present, an area of active investigation.

In summary, capecitabine in combination with preoperative RT achieves similar results, in terms of activity, to those reported with ci-5FU-RT, but with better treatment tolerance. The particularly favorable safety profile of this combination supports the rationale of combining capecitabine and RT with other available effective new drugs to improve these encouraging results further.

acknowledgements

The authors thank Daniela Michilin for editing the manuscript.

references

1. Swedish Rectal Cancer Trial. Improved survival with preoperative radiation in resectable rectal cancer. N Engl J Med 1997; 336: 980–987.
2. Kapiteijn E, Marijnen CA, Nagtegaal ID et al. Dutch Colorectal Cancer Group: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345: 638–646.
3. Minsky BD. Adjuvant therapy of rectal cancer. Semin Oncol 1999; 26: 540–544.
4. Krook JE, Moertel CG, Gunderson LL et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991; 324: 709–715.
5. Fisher B, Wolmark N, Rockette H et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 1988; 80: 21–29.

6. Gastrointestinal Tumor Study Group. Radiation therapy and fluorouracil with or without semustine for the treatment of patients with surgical adjuvant adenocarcinoma of the rectum. J Clin Oncol 1992; 10: 549–557.
7. O'Connell MJ, Martenson JA, Wieand HS et al. Improving adjuvant therapy for rectal cancer by combining protacted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994; 331: 502–507.
8. Bosset JF, Calais G, Mineur L et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. J Clin Oncol 2005; 23: 5620–5627.
9. Sauer R, Becker H, Hohenberger W et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351: 1731–1740.
10. Byefield JE, Calabro-Jones P, Klisak I et al. Pharmacologic requirements for obtaining sensitisation of human tumor cells in vitro to combined 5-fluorouracil or ftorarur and X-rays. Int J Radiat Oncol Biol Phys 1982; 8: 1923–1933.
11. Byefield JE, Frankel SS, Sharp TR et al. Phase I and pharmacologic study of 72-hours infused 5-fluorouracil and hyperfractionated cyclical radiation. Int J Radiat Oncol Biol Phys 1985; 11: 791–800.
12. Rich TA, Skibber JM, Ajani JA et al. Preoperative infusional chemoradiation therapy for stage T3 rectal cancer. Int J Radiat Oncol Biol Phys 1995; 32: 1025–1029.
13. Janjan NA, Crane C, Feig BW, Cleary K et al. Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 2001; 24: 107–112.
14. Smalley SR, Benedetti J, Williamson S et al. for the Southwest Oncology Group. Intergroup 0144- phase III trial of 5-FU based chemotherapy regimens plus radiotherapy (XRT) in postoperative adjuvant rectal cancer. Bolus 5-FU vs prolonged venous infusion (PVI) before and after XRT + PVI vs bolus 5-FU + leucovorin (LV) + levamisole (LEV) before and after XRT + bolus 5-FU + LV. Proc Am Soc Clin Oncol 2003; 22: 251 (Abstr 1006).
15. Miwa M, Ura M, Nishida M et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumors by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 1998; 34: 1274–1281.
16. Schuller J, Cassidy J, Dumont E et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000; 45: 291–297.
17. Van Cutsem E, Twelves C, Cassidy J et al. Oral capecitabine compared with intravenous 5-fluorouracil plus leucovorin (Mayo Clinic regimen) in patients with metastatic colorectal cancer: results of a large phase II study. J Clin Oncol 2001; 19: 4097–4106.
18. Sawada N, Ishikawa T, Sekiguchi F et al. X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. Clin Cancer Res 1999; 5: 2948–2953.
19. Dunst J, Reese T, Sutter T et al. Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. J Clin Oncol 2002; 20: 3983–3991.
20. Budman D, Meropol NJ, Reigner B et al. Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. J Clin Oncol 1998; 16: 1795–1802.
21. Mackean M, Planting A, Twelves C et al. Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. J Clin Oncol 1998; 16: 2977–2985.
22. Trotti A, Byhardt R, Stetz J et al. Common toxicity criteria: Version 2.0 – an improved reference for grading the acute effects of cancer treatment: Impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 13–47.
23. Miller AB, Hoogstraten, Staquet M et al. Reporting result of cancer treatment. Cancer 1981; 47: 207–214.
24. Sobin LH, Wittekind CH. UICC: TNM Classification of Malignant Tumors, 5th edition. New York, NY: Wiley-Liss 1997.
25. Ngan SY, Michael M, Mackay J et al. A phase I trial of preoperative radiotherapy and capecitabine for locally advanced, potentially resectable rectal cancer. Br J Cancer 2004, 91: 1019–1024.
26. Valentini V, Coco C, Picciocchi A et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 2002; 53: 664–674.
27. Gambacorta MA, Valentini V, Morganti AG et al. Chemoradiation with raltitrexed and oxaliplatin in preoperative treatment of stage II–III resectable rectal cancer: Phase I and II studies. Int J Radiat Oncol Biol Phys; 2004; 60: 139–148.
28. Dupuis O, Vié B, Lledo G et al. Capecitabine (X) chemoradiation (CRT) in the preoperative treatment of patients (pts) with rectal adenocarcinomas: a phase II GERCOR trial. Proc Am Soc Clin Oncol 2004; 23: 255 (Abstr 3538).
29. Dunst J, Reese T, Debus J et al. Phase-II study of preoperative chemoradiation with capecitabine in rectal cancer. Proc Am Soc Clin Oncol 2004; 23: 260 (Abstr 3558).
30. Cionini L, Cartei F, Manfredi B et al. Randomised study of preoperative chemoradiation (CT–RT) in locally advanced rectal cancer. Preliminary results. Int J Radiat Oncol Biol Phys 1999; 45 (Suppl 3): 178 (Abstr).
31. Kim JS, Kim JS, Cho MJ et al. Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2002; 54: 403–408.
32. Fernandes-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: 3016–3022.
33. Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004; 72: 15–24.
34. Crane CH, Skibber JM, Feig BW et al. Response to preoperative chemoradiation increase the use of sphincter-preserving surgery in patients with locally advanced low rectal carcinoma. Cancer 2003; 97: 517–524.
35. Aschele C, Friso ML, Pucciarelli S et al. A phase I-II study of weekly oxaliplatin, 5-fluorouracil continuous infusion and preoperative radiotherapy in locally advanced rectal cancer. Ann Oncol 2005; 16: 1140–1146.
36. Gerard JP, Chapet O, Nemoz C et al. Preoperative concurrent chemoradiotherapy in locally advanced rectal cancer with high-dose radiation and oxaliplatin-containing regimen: the Lyon R0-04 phase II trial. J Clin Oncol 2003; 21: 1119–1124.
37. Mehta VK, Cho C, Ford JM et al. Phase II trial of preoperative 3D conformal radiotherapy, procracted venous infusion 5-fluorouracil, and weekly CPT-11, followed by surgery for ultrasound-staged T3 rectal cancer. Int J Radiat Oncol Biol Phys 2003; 55: 132–137.
38. Rodel C, Grabenbauer GG, Papadopoulos T et al. Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. J Clin Oncol 2003; 21: 3098–3104.
39. Hofheinz R-D, von Gerstenberg-Helldorf B, Wenz F et al. Phase I trial of capecitabine and weekly irinotecan in combination with radiotherapy for neoadjuvant therapy of rectal cancer. J Clin Oncol 2005; 23: 1350–1357.