Evolution of 5-fluorouracil-based chemoradiation in the management of rectal cancer

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5-Fluorouracil (5-FU) is the most widely used agent for the management of colorectal cancer. Capecitabine is metabolized by three enzymatic actions, the last of which is mediated by thymidine phosphorylase, to produce 5-FU. Given the oral bioavailability of capecitabine as well as in-vitro and in-vivo findings showing higher expression of thymidine phosphorylase in tumor cells and xenografts compared with normal tissue, capecitabine is an evolving candidate in the management of colorectal cancer with antimetabolite-based therapy. An ideal radiosensitizing agent must balance oncological outcomes with adverse effects and feasibility of administration. This discussion addresses the evolving role of 5-FU in the management of rectal cancer in the neoadjuvant setting in combination with ionizing radiation. *Anti-Cancer Drugs* **22:311–316 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Rectal cancer is expected to affect 39 670 Americans in 2010 [1]. T1–2N0 rectal cancer has a 5-year survival of greater than 90% when treated exclusively with total mesorectal excision (TME) [2]. However, the 5-year survival substantially decreases to a dismal 15% in patients with T4N2 disease when treated with TME alone. Given this high rate of morbidity and mortality, chemoradiation was implemented as an adjunct to surgery to decrease the rate of local relapse. In the 1990s, neoadjuvant chemoradiation with 5-fluorouracil (5-FU)-based therapy emerged as the standard of care for patients with stages II–III rectal cancer, and has evolved since then [3]. This review discusses the evolution and current uses of fluoropyrimidines as a cytotoxic and radiosensitizing agent in the treatment of rectal cancer.

The cytotoxic and radiosensitizing properties of 5-fluorouracil

5-FU, combined with leucovorin, is the first and most widely used chemotherapeutic agent in all stages of colorectal cancer [4]. 5-FU inhibits thymidylate synthase (TS), resulting in impaired DNA synthesis (Fig. 1) [5]. Under normal conditions, deoxyuridine monophosphate (dUMP) forms a tripartite complex with tetrahydrofolate and TS. With the catalytic activity of TS, this forms deoxythymidine monophosphate (dTMP), a precursor for the nucleotide thymidine. 5-FU, which is metabolized to the active molecule 5-fluorodeoxyuridine monophosphate (FdUMP), prevents the synthesis of dTMP. FdUMP preferentially binds to TS and tetrahydrofolate, forming a tripartite complex that prevents the formation of dTMP. Leucovorin stabilizes this tripartite complex, further enhancing the cytotoxic activity of 5-FU [6]. Furthermore, FdUMP can be phosphorylated to 5-fluorodeoxyuridine monophosphate, which can be misincorporated into DNA and eventually lead to programmed cell death (apoptosis).

As in stage III colon cancer, adjuvant 5-FU is used as a cytotoxic agent to eradicate micrometastases and it has shown to improve the survival of patients with stages II–III rectal cancer [7]. However, when lower doses of 5-FU are administered with radiotherapy, there is a synergistic effect, known as radiosensitization. This phenomenon of 5-FU-mediated radiosensitization was first described in 1958 by Hiedelberger [8]. In-vitro studies of tumor cells show that there is an enhanced response to radiation when cells have been incubated with 5-FU. In the presence of fluoropyrimidines, the HT29 colon cancer cell line is radiosensitized because it expresses G1/S phase cyclins that are required to progress to the next phase in the cell cycle [9]. However, the SW620 cell line, which experienced less 5-FU-induced radiosensitization, did not express these cyclins and was arrested at the G1/S boundary in the presence of the drug. This showed that blocking entry into S phase decreases radiation sensitivity in the presence of 5-FU [10]. This was further corroborated when the SW620 cell line was transfected with the HPVE6 viral protein. Under normal circumstances, the E6 viral protein inactivates the retinoblastoma protein, causing a release of E2F and other transcription proteins that are required for progression into S phase. This allowed the cell to transcribe the genes for the necessary cyclins to progress from G1 to S phase of the cell cycle, rendering it a more radiosensitive

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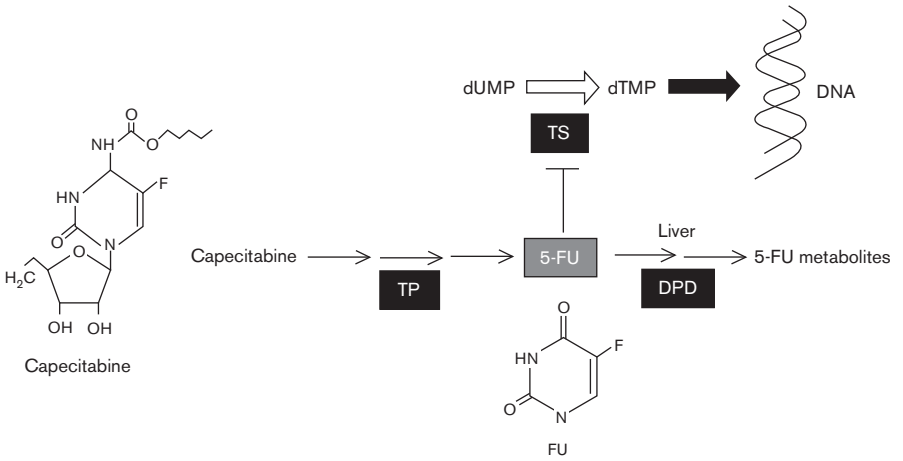
Fig. 1



Mechanism of actions of 5-flurouracil (5-FU) and capecitabine. DPD, dihydropyrimidine dehydrogenase; dUMP, deoxyuridine monophosphate; dTMP, deoxythymidine monophosphate; TP, thymidine phosphorylase; TS, thymidylate synthase.

phenotype. Thus, although all the antimetabolite drugs target DNA replication as a mechanism of action, 5-FU has unique properties as a radiosensitizer.

In addition, initial cell culture studies showed that tumor cells that are in the S phase are relatively radioresistant *in vitro* [11]. 5-FU has a cytotoxic effect on cells that are in the mid S phase; thus, 5-FU in combination with radiation is able to eliminate cells more effectively compared with ionizing radiation. The effects of 5-FU as a radiosensitizer seem to be beyond a shift in the phase of the cell cycle. The inhibition of DNA double-stranded bonds seems to be another mechanism by which 5-FU have its additive properties as a radiosensitizer [12].

The dosing of 5-FU could be increased to achieve maximal cytotoxic response. As 5-FU causes DNA dysfunction and it is S phase specific, increasing the infusion time of 5-FU increases the fraction of tumor cells that will be in the S phase, thus enhancing cytotoxicity [13]. Furthermore, the half-life of 5-FU is short and a continuous infusion during radiation could conceivably achieve superior radiosensitization. As a result, most modern day 5-FU regimens include infusional rather than bolus schedules. In a large North Central Cancer Treatment Group study, 660 patients with stage II or III rectal cancer were randomized to receive intermittent bolus injections or protracted infusions of 5-FU with postoperative radiation to the pelvis. Patients receiving infusional 5-FU had a superior overall survival (OS) and relapse-free survival [14]. At a median follow-up of 46 months, the relapse-free survival improved from 53% in the bolus injection group to 63% in the protracted infusion group ($P = 0.01$) and an OS from 60 to 70% ($P = 0.005$), respectively. However, there are no randomized prospective data in the neoadjuvant setting. In a small study of 33 patients, 21 patients received bolus 5-FU and 12 received continuous infusion. The rate of pathologically complete response (pCR) in the bolus arm was 10%, whereas it was 67% in the infusional arm ($P = 0.002$) [15]. Although there was a trend toward an improved survival, it was not clinically significant. Owing to the results of the North Central Cancer Treatment Group study, the guidelines for preoperative chemotherapy in rectal cancer include infusional 5-FU and leucovorin [16].

The cytotoxic and radiosensitizing properties of capecitabine

Capecitabine is an oral prodrug of 5-FU. After being absorbed by the mucosa of the small intestine, it undergoes a three-step enzymatic conversion into the active form of 5-FU (Fig. 1). It is considered as a tumor-specific therapy because the last enzyme required to complete the conversion of capecitabine into 5-FU is preferentially expressed in tumor cells relative to normal tissues [17]. This enzyme, thymidine phosphorylase (TP), is expressed in higher concentration by breast and colorectal tumor cells [18]. Given the slight differences in pharmacokinetics between 5-FU and capecitabine, the differences in the radiosensitizing properties may be due to tumor specificity or expression of TP.

Preclinical studies show that radiation can induce TP in tumor cells *in vitro*, thus increasing the rate of enzymatic conversion of capecitabine to 5-FU [19]. In one preclinical study, four of the five xenograft cell lines studied had an increase in TP when exposed to 2.5–5 Gy of ionizing radiation. In-vivo studies have corroborated these findings when total body irradiation of mice bearing colon cancer xenografts showed a 9.4-fold increase in TP within tumor cells, but no increase in levels in the liver. This additional

mechanism of radiosensitization made capecitabine an attractive alternative for phase I studies for the management of rectal cancer in the neoadjuvant setting [20].

Evolution of the treatment of rectal cancer

Adjuvant 5-FU-based chemoradiation was the mainstay of the treatment of locally advanced rectal adenocarcinoma until the 1990s. Multiple large clinical trials proved a statistically significant decrease in distant and local relapse in addition to a modest survival benefit [21–25] (Table 1). However, despite adjuvant chemoradiation, local recurrence rates ranged between 9 and 36% [26]. In an effort to mitigate the high rates of local recurrence, neoadjuvant radiation was explored. Preoperative therapy seemed to be a preferable option for a multitude of reasons [27]. First, surgically virgin tissue is better oxygenated, providing substantially higher therapeutic effects by ionizing radiation. Second, in the preoperative setting, there is often decreased exposure of the small bowel to ionizing radiation, which could lead to adhesions and radiation enteritis. The surgical benefits include downstaging tumor to facilitate sphincter preservation and the ability to excise irradiated bowel to perform an anastomosis with healthy bowel [28].

Two major trials, the Swedish study and the Medical Research Council/National Cancer Institute of Canada trial, noted over a 50% relative risk reduction in local relapse when patients were treated with preoperative radiation [29,30]. However, the OS outcomes in these two studies were not congruent and the surgical approach in these studies was different from the TME used today. In a third study, by the Dutch Colorectal Cancer Group, patients were randomly assigned to preoperative radiotherapy followed by TME versus TME alone [31]. At 2-year follow-up, patients that were randomized to neoadjuvant radiation and TME had a local recurrence of 2.4% compared with 8.2% in the TME alone arm ($P < 0.001$). Given the remarkable improvement in clinical outcomes, clinical trials examining the synergistic effect of neoadjuvant chemoradiation were inevitable.

Neoadjuvant 5-fluorouracil-based chemoradiation

Neoadjuvant chemoradiation was initially studied in patients who had T4 lesions that were deemed unresectable. In a nonrandomized trial, patients who were treated with neoadjuvant chemoradiation had a higher resectability rate than those who were treated with neoadjuvant radiation alone (90 vs. 64%) [32].

Multiple phase II studies showed the decrease in local relapse and/or increase in pCR rates [32–44] (Table 2). Since then, two large randomized trials, European Organisation for Research and Treatment of Cancer (EORTC 22921) and Fédération Francophone de la Cancérologie Digestive 9203, have studied the benefit of a combined modality treatment in the neoadjuvant setting [45,46]. In the EORTC 22921 study, 1011 patients were randomized to one of four arms, which included neoadjuvant radiation followed by surgery (arm 1), neoadjuvant chemoradiation followed by surgery (arm 2), neoadjuvant radiation followed by surgery and adjuvant chemotherapy (arm 3), or neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy (arm 4) [45]. A lower T and N staging was noted in the patients that underwent neoadjuvant chemoradiation. Furthermore, a pCR was observed in 13.7% of patients in the chemoradiation arm compared with 5.3% in the radiation only arm. On 5-year follow-up, the local recurrence rate was 17.1% (95% confidence interval, 12.3–21.9) in the neoadjuvant radiation arm and only 8.7% (95% confidence interval, 4.9–12.6) in the neoadjuvant chemoradiation arm [47]. However, the 5-year OS remained unaffected at 64.8 and 65.5% ($P = 0.84$), respectively.

In the Fédération Francophone de la Cancérologie Digestive 9203 trial, 762 patients were randomized to preoperative chemoradiation or radiation alone [46]. The pCR rate in the chemoradiation arm was 11.4 versus 3.6% in the arm that exclusively received radiation ($P < 0.0001$). The local recurrence rate at 5 years in the chemoradiation arm and radiation alone arm was 8.1 versus 16.5% ($P = 0.004$), respectively. Similar to EORTC 22921,

Table 1 **Relapse rates and survival rates of various adjuvant 5-fluorouracil-based chemoradiation regimens**

Study	Treatment arms	5-year local failure (%)	5-year distant failure (%)	5-year overall survival (%)	Citation
GITSG ($n=227$)	Surgery	25	34	43	[21]
	Surgery + chemotherapy	27	27	56	
	Surgery + radiation	20 ($P=0.08$)	30	52 ($P<0.05$)	
	Trimodality therapy	10	26	59	
NSABP R-01 ($n=555$)	Surgery	25	26	43	[22]
	Surgery + chemotherapy	21	24	53 ($P=0.05$)	
	Surgery + radiation	16 ($P=0.06$)	31	41	
NCCTG/Mayo ($n=204$)	Surgery + radiation	25	46	47	[23]
	Trimodality therapy	14 ($P=0.036$)	29 ($P=0.011$)	56 ($P=0.025$)	
Norwegian Adjuvant Rectal Cancer Study Group ($n=144$)	Surgery	30	39	50	[24]
	Trimodality therapy	12 ($P=0.01$)	33	64 ($P=0.05$)	
NSABP R-02 ($n=694$)	Surgery + chemotherapy	13	29	64	[25]
	Trimodality therapy	8 ($P=0.02$)	31	64 ($P=0.89$)	

GITSG, Gastrointestinal Tumor Study Group; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Table 2 Relapse rates and survival rates of various neoadjuvant 5-fluorouracil-based chemoradiation regimens

Study, citation	No. of patients	pCR (%)	Median follow-up	Local recurrence rate (%)	Distant recurrence rate (%)	DFS (%)	OS (%)
Minsky *et al.* [32]	21	10.0	NR	NR	NR	NR	NR
Chen *et al.* [36]	31	10.0	3 years	16	NR	NR	68
Rich *et al.* [43]	77	29.0	3 years	NR	NR	NR	83
Grann *et al.* [37]	32	9.0	3 years	0	NR	NR	60
Bosset *et al.* [33]	66	15.6	5 years	8	NR	NR	60
Kuchenmeister *et al.* [39]	22	NR	2 years	NR	NR	62	89
Grann *et al.* [37]	72	13.0	3 years	2	13	NR	95
Mehta *et al.* [40]	30	33.0	20 months	6	3	NR	NR
Ngan *et al.* [41]	82	16.0	NR	NR	NR	NR	NR
Tjandra *et al.* [44]	42	16.0	NR	NR	NR	NR	NR
Bozzetti *et al.* [34]	32	12.5	NR	NR	NR	NR	NR
Carau *et al.* [35]	33	15.5	14 months	12	12	NR	70
Nudelman *et al.* [42]	66	24.0	NR	NR	NR	NR	NR

DFS, disease-free survival; NR, not reported; OS, overall survival; pCR, pathologically complete response.

OS was approximately 67% in both groups. Although the benefit in OS is not proven, neoadjuvant chemotherapy is still considered optimal of locally advanced rectal cancer given the low rate of local relapse, better patient compliance, and possible decrease in surgical morbidities.

There is only one phase III trial comparing the benefit of neoadjuvant chemoradiation with adjuvant chemoradiation [48]. In this German trial, 421 patients were randomized to neoadjuvant or adjuvant chemoradiation. Although OS was not different, 5-year local relapse rates were significantly lower in the neoadjuvant arm versus the adjuvant arm (6 vs. 13%, respectively $P = 0.006$). Furthermore, patients were twice as likely to undergo sphincter preservation surgery in the neoadjuvant arm (39 vs. 19% $P = 0.004$). Although neoadjuvant chemoradiation does not confer a detectable benefit in OS, there is emerging evidence at present that pCR is a predictive factor in the long-term survival [49,50].

Neoadjuvant capecitabine chemoradiation

Capecitabine-based regimens are being evaluated as an alternative to 5-FU. Kim *et al.* [51] reported a pCR rate of 31% in one of the first phase II trials of capecitabine in cT3/4 and node-positive disease. Overall downstaging with this regimen was 84%. Since their initial trial in 2002, multiple phase II trials have been carried out to test the value of capecitabine with respect to pCR and toxicity profile [51–61] (Table 3). Das *et al.* [53] compared 89 patients who received capecitabine-based therapy with 89 individually matched (by T and N stage) patients who received 5-FU-based therapy. pCR rates in the capecitabine group was 21% compared with 12% in the 5-FU group ($P = 0.19$). Overall survival and 3-year relapse-free survival were 94 versus 98 and 89 versus 96%, respectively. Neither OS nor disease-free survival were clinically significant. In one of the largest phase II trials, 95 patients with potentially resectable rectal cancer were treated with capecitabine and concurrent radiotherapy [59]. The pCR rate was 12% and 92 of the 94 patients were able to undergo a complete resection. These rates are comparable with neoadjuvant 5-FU-based regimens.

Table 3 Complete pathologic response rates of neoadjuvant capecitabine-based chemoradiation regimens

Study, citation	No of patients	pCR rate (%)
Kim *et al.* [51]	45	91
Kim *et al.* [59]	95	12
Das *et al.* [53]	89	21
De *et al.* [54]	53	24
Krishnan *et al.* [60]	54	18
Velenik *et al.* [61]	57	9
Craven *et al.* [52]	70	9
Desai *et al.* [55]	30	26
Kim *et al.* [58]	133	17
Dunst *et al.* [56]	96	7
Elwanis *et al.* [57]	43	9

pCR, pathologically complete response.

Given the encouraging results with single-agent capecitabine, there are now multiple studies evaluating pCR rates and tumor downstaging with multidrug therapy. The most promising data are with a combination of capecitabine and oxaliplatin [62,63]. The largest phase II study includes 46 patients that were treated with capecitabine ($825\,mg/m^2$) at days 1–14 and oxaliplatin ($50\,mg/m^2$) at days 1 and 8 every 21 days [62]. The pCR rate for this regimen was 20.9%. Furthermore, combination therapy with capecitabine and irinotecan is being evaluated in phase I and II trials [64,65]. pCR rates seem to be comparable, but toxicity, namely, diarrhea and myelosuppression, seem to be higher when compared with 5-FU, capecitabine, and capecitabine/oxaliplatin regimens.

Currently, the data are limited with regard to phase III studies to validate the use of capecitabine or combinations including capecitabine for neoadjuvant therapy in rectal cancer. In a recent phase III study, 161 patients were randomized to either infusional 5-FU or capecitabine followed by radiation. Tumor downstaging occurred in 52% of patients in the capecitabine arm and 36% in the 5-FU arm ($P = 0.016$). Nodal downstaging was observed in 71 and 56% of patients ($P = 0.09$), respectively [66]. There was significantly less leukopenia in the capecitabine arm (25 vs. 35%; $P = 0.04$). However, there was a higher rate of hand–foot syndrome (31 vs. 2%; $P < 0.001$). Other toxicities, such as stomatitis, mucositis, diarrhea,

nausea, and vomiting were not significantly different in the two arms. There is an ongoing trial (R-04) by the National Surgical Adjuvant Breast and Bowel Project (*http://www.nsabp.pitt.edu/R-04.asp*, 2010). This trial is a four-arm study that randomizes patients to either neoadjuvant 5-FU/leucovorin or capecitabine, with or without oxaliplatin, in addition to concurrent radiation. It will compare locoregional recurrence, pCR rates, and sphincter preservation rates. This evidence shows that the R-04 trial might yield promising results in terms of superiority of capecitabine as a neoadjuvant agent compared with 5-FU.

Conclusion

Neoadjuvant chemoradiation is the mainstay of therapy for stages II and III rectal cancer. The main goal of this treatment is to downstage tumors, facilitate surgical intervention, and prevent local recurrence. Furthermore, emerging evidence in now suggesting that pCR is directly related to an improved survival [49,50]. Thus, the search for an ideal radiosensitizing agent must balance the best oncological outcomes with adverse effects and the feasibility of administration of the drug. Capecitabine seems to meet several of these requirements. First, 5-FU has a long-standing history of its clinical use. Second, capecitabine has the advantage of its oral administration and the potential to concentrate the compound in cancer cells. Finally, the oncological outcomes observed with capecitabine as measured by pCR seem to be promising.

Although infusional 5-FU or capecitabine are used both as cytotoxic and radiosensitizing agents, there continues to be a significant proportion of patients that do not have an adequate response to multimodality therapy. To enhance the efficacy of neoadjuvant treatment, combination therapy with oxaliplatin and irinotecan and alternative fluoropyrimidine therapy with capecitabine is being explored. Furthermore, there is an interest in the identification of molecular markers that can serve as predictive markers for response to neoadjuvant therapy.

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