



The results of recent clinical trials and the design of ongoing trials in the management of patients with metastatic colorectal cancer are reviewed.

J.J. Mahany, Jr. *Sunset*, 2002. Photograph. Healy, Alaska.

Metastatic Colorectal Cancer: Systemic Treatment in the New Millennium

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Background: Colorectal cancer (CRC) is common in North America. Metastatic disease is present at diagnosis in 30% of the patients, and approximately half of early-stage patients will eventually present with metastatic disease. Until recently, few chemotherapy options were available to treat metastatic CRC.

Methods: The authors review the results of recent clinical trials and the design of ongoing trials in the management of patients with metastatic colorectal cancer.

Results: Fluorouracil (5-FU) with leucovorin (LV) modulation has a marginal but positive effect on survival in those patients. The recent incorporation of irinotecan (CPT-11) and oxaliplatin for the management of advanced CRC has generated further improvement in survival. The development of oral fluoropyrimidines, mimicking continuous infusion 5-FU, is convenient. In randomized trials, capecitabine was equally effective to bolus 5-FU and LV in the management of metastatic CRC.

Conclusions: Recently completed or ongoing clinical trials to study novel targeting agents have initiated a new era of drug development. Anti-angiogenesis drugs, tyrosine kinase inhibitors, and epidermal growth factor blockers are among this new generation of agents with encouraging preliminary data. Randomized trials will determine the impact of these newer agents on survival and quality of life of patients with metastatic CRC.

Introduction

Colorectal cancer (CRC) is the most common gastrointestinal cancer in the United States.¹ Among all sites, CRC is the third most commonly diagnosed malignancy in both genders in North America. Projections

for 2003 estimate that 147,500 new cases of CRC will be diagnosed and 57,100 patients will die of this disease.¹ Approximately 30% of all patients with CRC have metastatic disease at diagnosis, and 50% of early-stage patients will eventually develop metastatic or advanced disease.² Chemotherapy is effective in pro-

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Submitted January 16, 2003; accepted March 31, 2003.

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No significant relationship exists between Dr Coutinho and the companies/organizations whose products or services are referenced in this article. Dr Rocha Lima receives grants/research support from Pfizer Inc, Aventis Pharmaceuticals Inc, and Eli Lilly and Co. He also receives honorarium from and is a consultant for these companies and GlaxoSmithKline.

longing survival and time to disease progression in patients with metastatic CRC.^{3,5}

The paucity of active agents in the treatment of CRC in the past resulted in extensive investigation of 5-fluorouracil (5-FU) and 5-FU-based combinations. This agent has been developed in many different schedules of administration. Modulation of 5-FU anticancer effects with leucovorin (LV) became one of the standard treatment regimens for metastatic colon cancer.

Additional pharmacologic strategies to enhance the effectiveness of 5-FU included combination with methotrexate, cisplatin, N-(phosphonacetyl)-L-aspartic acid (PALA), and interferon. Despite these attempts, no survival advantage was established until the advent of the newer cytotoxic drugs irinotecan and oxaliplatin.^{6,7} Additionally, improvement in convenience of drug administration has been achieved with the development of oral fluoropyrimidines for the treatment of metastatic CRC.

Table 1. — Phase III Trials of Second-Line Irinotecan (CPT-11) for Metastatic Colorectal Cancer

Author	No. of Patients	Design	1-Yr Survival	Median Survival
Cunningham ¹¹	279	CPT-11 + best supportive care vs Best supportive care	36% 13%	N/A
Rougier ¹²	267	CPT-11 vs 5-FU (de Gramont regimen)	45% 32%	10.8 mos 8.5 mos

Table 2. — Phase III Treatment Trials for First-Line Irinotecan (CPT-11) for Metastatic Colorectal Cancer

Author	No. of Patients	Design	Progression-Free Survival (mos)	Response Rate (%)	Median Survival (mos)
Saltz ¹⁴	683	<u>Arm 1</u> I 125 mg/m ² IV F 500 mg/m ² IV bolus L- 20 mg/m ² IV bolus Schedule: weekly for 4 wks every 6 wks	7.0	39	14.8
		<u>Arm 2</u> F 425 mg/m ² IV bolus L 20 mg/m ² IV bolus Schedule: d1-5 every 4 wks	4.3	21	12.6
		<u>Arm 3</u> I 125 mg/m ² IV Schedule: weekly for 4 wks every 6 wks	4.2 (P=.004)	21 (P=.001)	12.0 (P=.04)
Douillard ¹⁵	387	<u>Arm 1</u> I 80 mg/m ² F-2.3 g/m ² 24-hr CI L-500 mg/m ² Schedule: once weekly	6.7	49	17.4
		<u>Arm 2</u> I 180 mg/m ² d1 F 400 mg/m ² bolus and 600 mg/m ² 22-hr CI L 200 mg/m ² d1-2 Schedule: every 2 wks	4.4	31	14.1
		<u>Arm 2</u> F 2.6 g/m ² 24-hr CI L 500 mg/m ² Schedule: once weekly (AIO regimen*) F 400 mg/m ² bolus and 600 mg/m ² 22-hr CI L 200 mg/m ² d1-2 Schedule: every 2 wks (de Gramont regimen**)	4.4 (P=.001)	31 (P<.001)	14.1 (P=.031)

I = irinotecan (CPT-11)
 F = fluorouracil
 L = leucovorin
 IV = intravenous infusion
 CI = continuous infusion
 * Arbeitsgemeinschaft Internische Onkologie Cooperative German Group regimen¹⁶
 ** de Gramont regimen¹³

Newer Cytotoxic Drugs

Irinotecan

Irinotecan (CPT-11) is a semisynthetic derivative of the natural alkaloid camptothecin, a new class of anti-neoplastic agents. CPT-11 inhibits topoisomerase I (topo I) function by binding to the DNA-topo I cleavable complex. In vivo CPT-11 is enzymatically converted by carboxylesterase to its most active cytotoxic metabolite, 7-ethyl-10-hydroxy-camptothecin (SN-38).⁸ Colorectal tumors have higher levels of topo I than normal colon mucosa have. This difference in topo I levels may lead to a higher sensitivity of CRC cells to the cytotoxic effects of topo I inhibitors.⁹

CPT-11 was introduced into clinical practice based primarily on its phase II activity, with response rates (RRs) ranging from 13.3% to 21.7% in patients with advanced colon cancer refractory to 5-FU.¹⁰ Two phase III trials testing the efficacy of CPT-11 as second-line therapy for CRC patients previously treated with 5-FU have reported a survival advantage for CPT-11 (Table 1).^{11,12} In a randomized trial, 279 patients received either 350 mg/m² CPT-11 every 3 weeks plus supportive care or supportive care alone, in a 2:1 ratio. The 1-year survival rate of 36% vs 13% favored the CPT-11 arm ($P=.0001$).¹¹ A multicenter phase III trial studied 267 patients with metastatic colon cancer who had failed first-line 5-FU therapy.¹² Patients were randomized to either CPT-11 (350 mg/m² every 3 weeks) or infusional 5-FU according to the de Gramont regimen (400 mg/m² 5-FU intravenous [IV] bolus followed by 600 mg/m² continuous infusion over 2 days every 2 weeks, plus folinic acid).¹³ The 1-year survival rate was 45% and 32% for the CPT-11 arm and the 5-FU arm, respectively ($P=.03$). The median survival was 10.8 months in the CPT-11 group and 8.5 months in the 5-FU group. Based on these two second-line studies, use of the combination of CPT-11, LV, and 5-FU for second-line treatment in patients with 5-FU-refractory, advanced CRC was justified at that time.

The demonstrated benefits for CPT-11 as second-line therapy for CRC led to the evaluation of the combination CPT-11/5-FU/LV as first-line treatment in advanced colon cancer. Two phase III trials showed the superiority of the new regimen over 5-FU and LV (Table 2). Saltz et al¹⁴ randomized 683 patients with metastatic CRC without previous treatment to one of three arms: (1) CPT-11/bolus 5-FU/LV (IFL) weekly for 4 weeks on a 6-week cycle, (2) 5-FU plus LV daily for 5 days once every 4 weeks, or (3) CPT-11 alone weekly for 4 weeks on a 6-week cycle. Median survival favored the IFL combination: 14.8 months vs 12.6 months and 12.0 months, respectively ($P=.04$). The

Table 3. — Toxicity Profile for the IFL Regimen

Author	Diarrhea Grade 3/4	Mucositis Grade 3/4	Neutropenia Grade 3/4
Saltz ¹⁴			
IFL	22.7%	2.2%	24.0%
FL	13.2%	16.9%	42.5%
Douillard ¹⁵			
IFL	44.4% / 13.1%	4.1%	28.8% / 46.2%
FL	25.6% / 5.6%	2.3% / 2.1%	2.4% / 13.4%
I = irinotecan (CPT-11) F = fluorouracil L = leucovorin			

toxicity profile also favored the IFL group, except for diarrhea (Table 3). Douillard et al¹⁵ randomized 387 previously untreated patients with advanced CRC to 5-FU/LV, using either the de Gramont regimen (every 2 weeks) or the Arbeitsgemeinschaft Internische Onkologie regimen (once weekly)¹⁶ with or without CPT-11 (Table 2). Survival was significantly longer in the CPT-11 group: 17.4 months vs 14.1 months ($P=.031$). The median duration of treatment was not affected by the higher frequency of adverse events that occurred in the CPT-11 group compared with the group not receiving CPT-11 (Table 3).

More serious toxicity issues were raised in April 2001 when the External Data Monitoring Committee of the North Central Cancer Treatment Group (NCCTG) identified an unexpected number of deaths occurring within the first 60 days of study entry onto protocol N9741 with the combination of bolus IFL.¹⁷ Fourteen deaths (4.8%) occurred in the IFL arm, 5 deaths (1.8%) in the 5-FU, LV, and oxaliplatin arm (de Gramont regimen), and 5 (1.8%) in the oxaliplatin plus CPT-11 arm. In another multicenter phase III trial in which the IFL regimen was randomly compared to 5-FU plus LV (Roswell Park regimen) as adjuvant therapy in CRC, 14 (2.2%) deaths in the IFL group vs 5 (0.8%) deaths in the 5-FU plus LV group were reported.^{17,18} The enrollment to these trials was temporarily suspended. A panel of experienced investigators gathered and recommended more aggressive supportive therapy. Close monitoring, withholding therapy in the presence of unresolved drug-related toxicity, and aggressive use of antidiarrhea medications and antibiotics were encouraged. In addition, the review of the early toxic deaths from previous phase III trials with the Mayo Clinic and Roswell Park schedules of 5-FU and LV suggested that the toxicity encountered with IFL at the Cancer and Leukemia Group B (CALGB) and NCCTG trials was not excessive.¹⁹

Oxaliplatin

Oxaliplatin is a novel diaminocyclohexane platinum agent that has a mechanism of action similar to that of platinum derivatives, but it is active against human colon cancer cell lines and is synergistic with 5-FU. The drug is a potent inhibitor of DNA synthesis.²⁰ Its clinical tox-

icity is distinct from other platinum drugs in that it causes a cold-related dysesthesia and a dose-limiting cumulative peripheral sensory neuropathy that usually regresses after treatment withdrawal. Unlike cisplatin, renal toxicity is not a major concern with oxaliplatin; unlike carboplatin, only minimal bone marrow toxicity and little alopecia have been reported with oxaliplatin.²¹

Table 4. — Selected Studies of FOLFOX in Relapsed Colorectal Cancer

Author	No. of Patients	Regimen	Dose/Schedule	Response Rate (%)	Median Progression-Free Survival/Overall Survival	Grade 3/4 Toxicity (%)
de Gramont ²² (1997)	113	FOLFOX 1 (second-line treatment)	O 130 mg/m ² every 2 cycles plus L 500 mg/m ² 2 hrs d1 followed by F 1.5-2 g/m ² in 22 hrs for 2 days Schedule: every 2 wks	29.2	6 mos/11 mos	Global: 54
de Gramont ²³ (1997)	46	FOLFOX 2 (second-line treatment)	O 100 mg/m ² 2 hrs d1 plus L 500 mg/m ² 2 hrs followed by F 1.5-2 g/m ² 24 hrs for 2 days Schedule: every 2 wks	46	7 mos/17 mos	Neuropathy: 9
Andre ²⁴ (1998)	30	FOLFOX 3 (second-line treatment)	O 85 mg/m ² plus L 500 mg/m ² plus F 1.5-2 g/m ² in 22 hrs d1-2 Schedule: every 2 wks	20	26 wks/57 wks	Neuropathy: 90
de Gramont ²⁵ (2000)	420	FOLFOX 4 (first-line treatment)	<u>Arm 1</u> O 85 mg/m ² d1 plus L 200 mg/m ² d1-2 F 400 mg/m ² bolus d1-2 and 600 mg/m ² /d 22-hr infusion d1-2 Schedule: every 2 wks	49.5	9 mos/16.2 mos	Neurotoxicity: 18.2 Neutropenia: 41.7 Diarrhea: 11.9
			<u>Arm 2</u> L 200 mg/m ² /day d1-2 F 400 mg/m ² bolus d1-2 and 600 mg/m ² /d 22-hr infusion d1-2 Schedule: every 2 wks	28.6	6.2 mos/14.7 mos	Neurotoxicity: 0 Neutropenia: 5.3 Diarrhea: 5.3
Maindrault-Goebel ²⁶ (1999)	60	FOLFOX 6 (second-line treatment)	O 100 mg/m ² plus L 400 mg/m ² in 2 hrs d1 followed by F 400 mg/m ² bolus and 2.4-3 g/m ² in 46 hrs Schedule: every 2 wks (36% received >90% of the O dose)	27	5.3 mos/10.8 mos	Neuropathy: 16 Neutropenia: 24 Diarrhea: 7 Global: 46
Maindrault-Goebel ²⁷ (2001)	48	FOLFOX 7 (second-line treatment)	O 130 mg/m ² plus L 400 mg/m ² in 2 hrs d1 followed by F 400 mg/m ² bolus and 2.4 g/m ² in 46 hrs Schedule: every 2 wks (64% received 90% of the O dose)	42	6 mos/16.1 mos	Neuropathy: 15 Neutropenia: 9 Diarrhea: 11 Global: 38

O = oxaliplatin
L = leucovorin
F = fluorouracil
FOLFOX = oxaliplatin, fluorouracil, and leucovorin

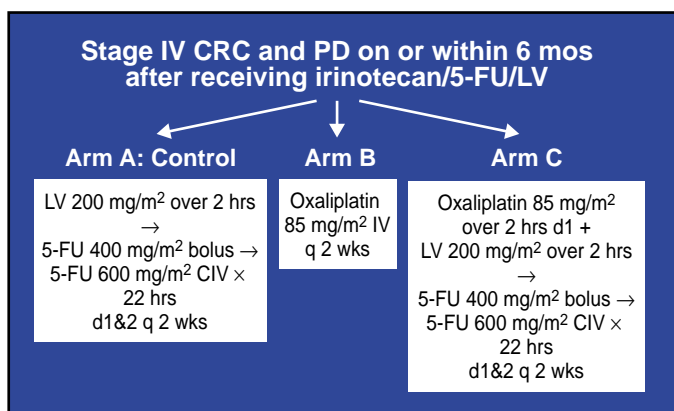


Fig 1. — 5-FU/LV vs oxaliplatin vs 5-FU/oxaliplatin in patients with recurrent CRC following IFL (EFC 4584: The US Pivotal Trial). Reprinted with permission from Sanofi-Synthelabo Inc. CIV = continuous intravenous infusion, PD = progressive disease.

Several phase II studies²²⁻²⁸ demonstrated a 20% to 50% RR with the combination of oxaliplatin plus 5-FU and LV as second-line treatment in patients with relapsed CRC (Table 4). These data should be interpreted with caution since all of these studies are small and subject to patient selection. A more robust study has been recently reported that resulted in the approval of oxaliplatin in combination with 5-FU and LV by the Food and Drug Administration (FDA) as second-line therapy of patients with CRC previously treated with IFL (Fig 1) and probably represents more realistic efficacy data.²⁹ In this trial, a bolus/infusional regimen of 5-FU plus LV was compared to single-agent oxaliplatin and to the combination of bolus/infusional 5-FU plus LV and oxaliplatin at the doses and schedule of FOLFOX 4. A total of 459 of 821 enrolled patients were evaluable at the time of the planned interim analyses, which were designed to evaluate objective RR, time to tumor progression (TTP), and alleviation of tumor-related symptoms but not the primary endpoint of the trial, survival. The FOLFOX 4 regimen was superior to the bolus/infusional 5-FU plus LV control arm and also to single-agent oxaliplatin. The objective RR of 9.9% and the TTP of 4.6 months for FOLFOX 4 was superior to the RR of 1.3% and the TTP of 1.6 months for single-agent oxaliplatin and also superior to the RR of 0% and the TTP of 2.7 months for the bolus/infusional 5-FU plus LV.

In a phase II trial of 38 chemotherapy-naïve patients with CRC, single-agent oxaliplatin at 130 mg/m² IV in a 21-day-cycle resulted in an RR of 24.3%.³⁰ Randomized trials assessing the impact of the combination of oxaliplatin, 5-FU, and LV as first-line treatment for metastatic CRC have been performed.^{25,31} The European Organization for Research and Treatment of Cancer (EORTC) multicenter randomized phase III trial included 200 patients receiving a 5-day course of chronomodulated

IV-infusion 5-FU 700 mg/m² per day and LV 300 mg/m² per day, with half of these patients also receiving oxaliplatin.³¹ The objective RR was 16% and 53%, respectively, favoring the oxaliplatin arm ($P < .0001$), but no statistically significant benefit in overall survival was achieved. A study by de Gramont et al²⁵ randomized 420 patients to receive either 5-FU plus LV or the same regimen with the addition of oxaliplatin (FOLFOX 4) (Table 4). The oxaliplatin arm resulted in higher RRs (49.5% vs 28.6%) and improved median progression-free survival (9.0 months vs 6.2 months) ($P = .0001$). Overall survival was not statistically different despite a numerical advantage for the group receiving oxaliplatin (16.2 months vs 14.7 months) ($P = .12$). The lack of a statistically significant survival benefit favoring the addition of oxaliplatin to 5-FU and LV for the first-line therapy for patients with metastatic CRC in these two studies delayed the FDA approval of oxaliplatin in the United States.

Oxaliplatin vs CPT-11 as First-Line Therapy of CRC

The NCCTG phase III trial N9741 has been reported in abstract form.³² This trial was initially designed to have 6 arms and was eventually reduced to a 3-arm trial (Fig 2) comparing FOLFOX 4, IFL (Saltz schedule), and the combination of oxaliplatin and CPT-11 (Wasserman schedule)³³ for the management of metastatic CRC. The overall survival of 18.6 months and 14.1 months favored FOLFOX 4 over IFL. While increased efficacy with oxaliplatin may be the variable responsible for this statistically significant improvement in survival, the difference in the infusion of 5-FU (bolus infusion in the IFL regimen and prolonged infusion in FOLFOX 4) and the imbalance in second-line therapy (a high percentage of patients received second-line irinotecan chemotherapy in the FOLFOX 4 arm while few patients

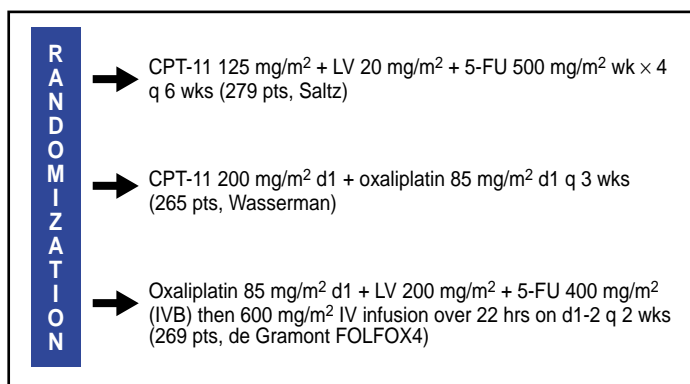


Fig 2. — Intergroup Protocol 89804 in advanced CRC (N9741). From Goldberg RM, Morton RF, Sargent DJ, et al. N9741: oxaliplatin (oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Initial toxicity and response data from a GI Intergroup study. *Proc Annu Meet Am Soc Clin Oncol*. 2002;511. Abstract. Adapted with permission of the American Society of Clinical Oncology.

Table 5. — Randomized Trials With FOLFOX and IFL

Regimen	NCCTG 9741 ³²		Tournigand ³⁴	
	IFL (Saltz)	FOLFOX 4	FOLFIRI	FOLFOX 6
Population Size	264	267	106	109
Overall Survival (mos)	14.1	18.6	20.4	21.5
Progression-Free Survival (mos)	6.9	8.8	8.5	8.1
Overall Response Rate (%)	29.0	38.0	56.0	54.0
Second-Line Irinotecan (%)	—	52.0	—	62.0
Second-Line Oxaliplatin (%)	17.0	—	74.0	—

in the IFL arm received second-line oxaliplatin) may be the alternative explanations for the better efficacy results favoring FOLFOX 4 over IFL in this randomized phase III trial. In addition, the discrepancy between TTF (5 months in both arms) and TTP (8.8 months and 6.9 months favoring FOLFOX 4 over IFL) (Table 5) may be a consequence of a higher percentage of patients stopping the FOLFOX 4 arm due to toxicity and starting on therapy with irinotecan without progression.

A phase III study in which both irinotecan and oxaliplatin were paired with a similar infusion schedule of 5-FU/leucovorin has been performed as first-line therapy for patients with metastatic CRC.³⁴ A crossover design allowed both groups to have similar exposure to both treatment arms as first- and second-line therapy. In this trial, patients were randomized to receive either FOLFIRI (prolonged infusion 5-FU plus LV plus CPT-11) to CRC progression followed by FOLFOX 6 as second-line therapy or the alternative sequence of FOLFOX 6 to CRC progression followed by FOLFIRI. The RRs to first-line therapy were similar (57.5% for the FOLFIRI arm and 56% for the FOLFOX 6 arm) (Table 5). However, the second-line therapy with FOLFOX 6 resulted in higher activity than with FOLFIRI (21% vs 7%). Despite the difference in second-line RRs, no advantage in survival was observed for either sequence. This trial suggests that CPT-11 or oxaliplatin in combination with prolonged infusion 5-FU and LV appears to have similar efficacy results in the management of metastatic CRC. Therefore, the sequence of administration should be determined by reasons other than efficacy (eg, convenience or comorbidities).

Oral Fluoropyrimidines

The pharmacokinetics of the oral fluoropyrimidines may mimic the pharmacokinetics of continuous infusion 5-FU.³⁵ Among humans, 5-FU has a variable absorption when given orally because the intestinal mucosa contains different concentrations of dihydropyrimidine dehydrogenase (DPD), the enzyme that

catabolizes more than 80% of orally administered 5-FU. Patients with high intestinal DPD have a higher percentage of 5-FU inactivation, thus leading to lower plasma drug concentrations. In contrast, patients with DPD deficiency are likely to have higher plasma levels of 5-FU and consequently more 5-FU-related toxicity. The difficulty of delivering 5-FU orally can be overcome by administering 5-FU pro-drugs that can be absorbed as intact molecules and then converted to 5-FU after intestinal absorption. Alternatively, the addition of DPD inhibitors to oral 5-FU may also be efficacious in increasing the intestinal absorption of 5-FU.³⁶

The toxicity profile of oral fluoropyrimidines resembles the toxicity of prolonged infusion 5-FU rather than the bolus infusion. Neutropenia occurred more frequently with bolus infusion 5-FU (31% of patients) than with continuous infusion 5-FU (4% of patients) ($P<.0001$). However, hand-foot syndrome occurred less often with bolus (13%) than continuous (34%) infusion ($P<.0001$).^{37,38} The suggested higher efficacy of prolonged infusion over the bolus 5-FU infusion in a meta-analysis,³⁹ as well as the convenience of oral fluoropyrimidines, increases the interest in developing agents such as tegafur plus uracil (UFT), capecitabine, eniluracil, S-1, and emitefur (BOF-A2).

UFT

UFT is a combination of uracil (a competitive inhibitor of DPD) and tegafur (a prodrug of 5-FU) in a fixed molar ratio of 4:1, to provide sustained levels of 5-

Table 6. — Randomized Phase III Trials Comparing Tegafur and Uracil (UFT) Plus Leucovorin (LV) With 5-FU Plus LV in First-Line Treatment for Metastatic Colorectal Cancer

Author	No. of Patients	Response Rate (%)		P Value
		UFT + LV	5-FU + LV	
Carmichael ⁴⁰	380	11.0	9.0	.59
Douillard ⁴¹	816	11.7	14.5	.232

Table 7. — Randomized Phase III Trials Comparing Capecitabine With 5-FU Plus Leucovorin (LV) in First-Line Treatment of Metastatic Colorectal Cancer

Author	No. of Patients	Response Rate (%)		P Value
		Capecitabine	5-FU + LV	
Twelves ⁴⁶	602	26.6	17.9	.013
Hoff ⁴⁷	605	24.8	15.5	.0005

FU. Two large randomized phase III trials compared the oral regimen of UFT plus LV to IV 5-FU and LV as first-line treatment for metastatic CRC (Table 6).^{40,41} The first trial enrolled 380 patients to oral UFT 300 mg/m² per day plus oral LV 90 mg per day (ORZEL) for 28 days every 35-day cycle or to 5-FU 425 mg/m² per day plus LV 20 mg/m² per day IV for 5 days every 28-day cycle. The responses of 11% for ORZEL vs 9% for 5-FU plus LV were comparable ($P=.593$).⁴⁰ The second randomized trial enrolled 816 patients and studied the same dose and schedules of ORZEL and 5-FU. This trial also reported comparable results.⁴¹ Thus far, the FDA has not approved UFT for the treatment of CRC.

Eniluracil

Eniluracil is a pyrimidine analog and a potent irreversible direct inactivator of DPD. Following an oral dose of 10 mg, there is a rapid cessation of DPD activity in tumor and normal tissues. The drug has been used in combination with an oral formulation of 5-FU. Phase III studies have been performed comparing eniluracil plus oral 5-FU and IV 5-FU plus LV. None of the studies demonstrated any survival benefit for the group taking eniluracil plus oral 5-FU.^{42,43} The development of eniluracil has been discontinued.

S-1

S-1 (BMS 247616) is an orally bioavailable 5-FU pro-drug. It is composed of tegafur plus two modulators: a DPD inhibitor (5-chloro-2,4-dihydroxypyridine [CDHP]), more potent than uracil, and oxonic acid, an inhibitor of phosphoribosyl pyrophosphate transferase (an enzyme located in the gastrointestinal tract that causes decreased 5-FU incorporation into cellular RNA).⁴⁴ To our knowledge, to the date of submission of this manuscript, no phase III trials studying the efficacy of S-1 in CRC have been reported.

Capecitabine

Capecitabine, a fluoropyrimidine carbonate, is the only oral fluoropyrimidine commercially available in the United States for the treatment of metastatic CRC. This 5-FU pro-drug is absorbed intact through the gas-

trointestinal mucosa and is metabolized in the liver to 5'-deoxy-5-fluorocytosine and to doxifluridine. Doxifluridine is then converted by the enzyme thymidine phosphorylase, which is found in high concentrations in tumor tissue, to 5-FU. A phase II trial suggested that capecitabine at a dose 2.5 g/m² p.o. daily for 14 days followed by a 7-day rest period as a monotherapy regimen be further explored in subsequent clinical trials. The trial also concluded that the addition of LV to capecitabine does not result in a clear benefit to single-agent capecitabine.⁴⁵

To our knowledge, the effectiveness of capecitabine compared to infusional 5-FU has not been studied in randomized trials. Two large randomized phase III trials comparing capecitabine with IV bolus 5-FU and LV have been performed (Table 7). Twelves et al⁴⁶ randomized 602 patients with advanced or metastatic CRC to oral capecitabine at a total daily dose of 2,500 mg/m², divided into 2 daily doses, for 2 weeks followed by 1 week of rest or to IV 5-FU/LV on the Mayo Clinic regimen. The overall RR was higher for the capecitabine group (26.6%) compared with the 5-FU/LV group (17.9%) ($P=.013$). Median progression-free and overall survivals were equivalent in both groups. The study emphasized that 34.3% more patients in the 5-FU/LV group were hospitalized for treatment-related adverse events. Hoff et al⁴⁷ published the results of the other large randomized phase III trial where 605 patients received either capecitabine or 5-FU/LV in the same schedule and doses as the aforementioned trial. Higher RRs were again demonstrated favoring the capecitabine group, but no statistical dif-

Table 8. — Combinations of Capecitabine With Irinotecan- or Oxaliplatin-Based Regimens

Author	Regimen	Phase	Overall Response Rate
Schleucher ⁴⁸ (2001)	Irinotecan weekly + capecitabine	I	42%
Kerr ⁴⁹ (2002)	Irinotecan every 3 wks + capecitabine	I/II	48%
Cassata ⁵⁰ (2001)	Irinotecan (2 schedules) + capecitabine	II	71%
Tabernero ⁵¹ (2002)	Oxaliplatin + capecitabine	II	55%
Jordan ⁵² (2002)	Capecitabine/irinotecan vs capecitabine/oxaliplatin	II randomized	37.5% vs 41.2%

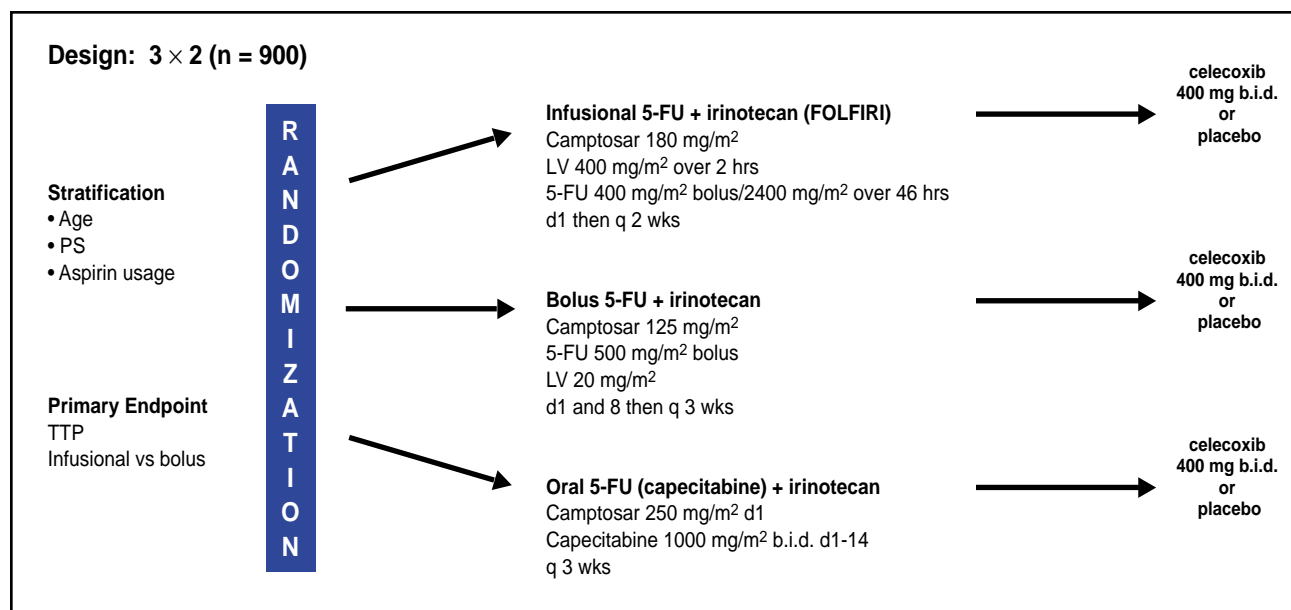


Fig 3. — BICC-C: first-line CRC trial. Reprinted with permission from Pharmacia Oncology.

ferences in time to disease progression or overall survival were demonstrated between the two groups.

Ongoing or recently completed trials to access the feasibility and efficacy of capecitabine combined with CPT-11 or oxaliplatin may result in more convenient regimens without compromising efficacy (Table 8).⁴⁸⁻⁵² Phase III studies are ongoing or planned in the first-line treatment of metastatic CRC testing the efficacy of capecitabine with CPT-11 compared to IFL or FOLFIRI (Fig 3).^{53,54}

Raltitrexed

Raltitrexed, a water-soluble quinazoline antifolate, is a specific inhibitor for thymidylate synthase (TS). This drug is administered by IV infusion at a dose of 3 mg/m² every 3 weeks and has been compared with 5-FU plus LV (Mayo regimen or Machover regimen) as first-line treatment in three randomized trials.⁵⁵⁻⁵⁷ All trials produced similar RRs that ranged from 14% to 19% for raltitrexed and from 15% to 18% for 5-FU plus LV. Preliminary results in one of the three randomized trials suggest that raltitrexed may be inferior to infusional 5-FU in terms of treatment-related deaths, progression-free survival, and quality of life.⁵⁸ Comparing raltitrexed with 5-FU/LV in the de Gramont schedule and the Lokich schedule, the RRs were 20%, 24%, 26%, respectively. Serious adverse events were reported more frequently (18%) in the raltitrexed group compared with 3% in de Gramont group and 12% in the Lokich group. In addition, the group given raltitrexed had poorer quality of life outcomes. There was no difference in survival among the 3 groups.

Pemetrexed

Pemetrexed is a multitarget antifolate that inhibits at least three enzymes: TS, dihydrofolate reductase, and glycinamide ribonucleotide (GAR) formyltransferase. These enzymes are involved in the folate metabolism and DNA synthesis. The RRs with single-agent pemetrexed in patients with CRC are comparable to those with bolus 5-FU and LV.^{58,59} Pemetrexed is undergoing FDA review for approval in the management of malignant mesothelioma. Additional studies in CRC are awaited.

Chemotherapy as Adjunct to Surgery in CRC Liver Metastases

Surgical resection, if possible, is the most effective treatment modality for potential long-term survival in CRC patients with liver metastases.⁶⁰ The role of this approach was evaluated in a 60-patient study where patients had multiple liver metastases removed (20 patients) or solitary liver metastases operated on (40 patients) at the time of the primary cancer colonic surgery.⁶¹ Fifteen of the 36 eligible patients having a solitary liver metastases removed survived 10 years or more after the surgery. None of the 20 patients with multiple lesions excised lived for 5 years or more. These results were better than the observed outcome in 60 other patients who did not have their hepatic metastases (comparable in size and number) resected at the time of colonic surgery. None of the patients in this last group were alive at 5 years.

The 5-year survival of 2,500 patients undergoing aggressive surgical excisions for hepatic metastases

(including single and multiple liver metastases) varies from 20% to 39%.⁶² Other smaller reviews resulted in similar 5-year survival rates for patients undergoing metastasectomy of CRC liver metastases.^{63,64} Unfortunately, only 10% to 25% of patients with liver metastasis are suitable for resection at the time of initial staging.⁶³ The role of more modern interventional techniques including cryosurgery, radiofrequency ablation, portal vein embolization, and two-stage hepatectomy in increasing the percentage of CRC patients with liver metastases to become candidates for curative surgery is the subject of intense ongoing studies. This discussion is beyond the scope this review.

The application of chemotherapy to decrease the bulk of metastatic disease and convert unresectable patients into potential candidates to curative surgery has also been explored.^{60,65} The combination of 5-FU, LV, and oxaliplatin has been further studied in this setting. Reported partial responses in more than 50% of treated patients and consequent conversion of “unresectable” to “resectable” tumors in more than half of the studied patients puts this approach in focus for the management of liver metastasis.^{60,65}

Another consideration is to test upfront chemotherapy in patients with liver metastases from CRC who are believed to be surgical candidates for an R0 (microscopic negative margins) resection at baseline. This approach is attractive but should be tested first in a clinical trial since it is not devoid of risk for cancer progression, beyond a future R0 surgical intervention, in patients who may progress on chemotherapy. In our practice, we recommend surgery as the primary modality for patients with CRC liver metastases who are potential candidates for R0 surgical intervention based on the preoperative workup. Upfront chemotherapy is reserved for patients believed to have unresectable metastases. An EORTC phase III trial comparing surgery

for metastatic liver disease with and without neoadjuvant FOLFOX in patients with resectable colorectal liver metastases is ongoing.

Postoperative hepatic artery infusion of 5-FU and LV in patients undergoing resection for colorectal metastases has not resulted in improvement in survival.⁶⁶ However, the use of intrahepatic floxuridine (FUDR) and dexamethasone plus systemic 5-FU and LV compared to systemic 5-FU and LV resulted in a 2-year survival rate of 86% compared to 72% in the group given systemic therapy alone ($P=.03$).⁶⁷ The median survival was 72.2 months in the combined-therapy group and 59.3 months in the systemic therapy-alone group. After 2 years, the rates of survival free of hepatic recurrence were 90% in the systemic plus intrahepatic chemotherapy group and 60% in the systemic chemotherapy-alone group ($P<.001$). To our knowledge, no studies have been conducted regarding the value of postoperative modern systemic chemotherapy like FOLFOX or FOLFIRI with or without hepatic artery infusion after colorectal cancer metastatic resection.

Despite progress in the treatment of metastatic CRC with the newer cytotoxic drugs, the proportion of complete responses is small, and cures in patients with metastatic, surgically unresectable disease are anecdotal. Advances in the understanding of the biology of this disease have resulted in the development of molecular targeting agents that can take the treatment of CRC to the next level.

Angiogenesis Inhibitors

Angiogenesis plays an important role in the growth and metastasis of many cancers. The antiangiogenic drugs can be divided into several categories, including growth factor inhibitors, endothelial cell signal transduction inhibitors, inhibitors of endothelial cell prolifer

Table 9. — Phase II Trials of Bevacizumab in Advanced Colorectal Cancer

Author	Regimen	No. of Patients	Response Rate	Time to Progression	Median Survival
Kabbinavar ⁶⁸ (2003)	Arm 1 BV (5 mg/kg) + 5-FU + LV	104	40% ($P=.029$)	9.0 mos	21.5 mos
	Arm 2 BV (10 mg/kg) + 5-FU + LV		24% ($P=.43$)	7.2 mos	16.1 mos
	Arm 3 (control) 5-FU + LV		17%	5.2 mos	13.8 mos
Giantonio ⁶⁹ (2002)	BV + IFL	Ongoing	Ongoing	Ongoing	Ongoing

BV = bevacizumab
LV = leucovorin
5-FU = 5-fluorouracil

Table 10. — Phase I and II Trials of Cetuximab (C225)

Author	No. of Patients	Treatment	Phase	Partial Response	Line of Treatment	Previous Treatment Status
Saltz ⁸⁰ (2001)	121	C225 + CPT-11	II	22.5%	2nd	Refractory to CPT-11/5-FU
Saltz ⁸¹ (2002)	57	C225 alone	II	11.0%	2nd	Refractory to CPT-11/ 5-FU
Rosenberg ⁸² (2002)	27	C225 + CPT-11 + 5-FU + LV	II	44.0% (11 patients)	1st	Untreated patients
Ongoing		C225 + FOLFOX 4 vs FOLFOX 4	III		2nd	Refractory to CPT-11 combination

eration, inhibitors of matrix metalloproteinases, and inhibitors of endothelial cell survival.

CRC has been shown to express elevated levels of the angiogenic factor VEGF (vascular endothelial growth factor). Expression of VEGF in primary tumor tissue is correlated with poor outcome in colon cancer, and plasma levels of VEGF have been correlated with stage, progression of disease, and response to chemotherapy. Some antibodies targeting VEGF have been tested. Among these, bevacizumab (BV), a recombinant humanized monoclonal antibody targeting VEGF, is in further development in CRC. A phase II trial recently published by Kabbinar et al⁶⁸ studied the combinations of low- and high-dose BV with 5-FU plus LV compared with 5-FU plus LV alone in patients with previously untreated metastatic CRC. The results for RR and TTP were numerically higher in the low-dose BV arm (Table 9). The small number of patients and imbalances among the arms may be one of the explanations for the more attractive efficacy results observed with the low-dose BV. Nonetheless, the results from this trial are promising. Further development of BV in combination with irinotecan or oxaliplatin is either ongoing⁶⁹ or being planned for patients with CRC.

Thalidomide has also been studied in metastatic CRC. Early reports suggest that thalidomide may decrease the incidence of CPT-11-induced diarrhea.⁷⁰ Govindarajan et al⁷¹ reported a 40% RR in 20 chemotherapy-naive patients with the combination of thalidomide and CPT-11. In this trial, thalidomide appears to enhance the response to CPT-11. However, in an ongoing phase II trial, single-agent thalidomide in 10 patients with previously treated CRC has resulted in no responses.⁷²

Epidermal Growth Factor Inhibitors

Tumor growth depends on the activation of cell membrane receptors that control the intracellular signal transduction pathways for proliferation, adhesion, and motility. Epidermal growth factor receptor (EGFR)

is a glycoprotein receptor that is expressed on normal epithelium and is sometimes overexpressed in a variety of epithelial tumors, including colorectal carcinoma. The overexpression of EGFR correlates with poor response to treatment, disease progression, and poor survival. Inhibition of EGFR signaling with an EGFR antibody is accompanied by a reduction in the level of DNA-dependent protein kinase and its activity in the nucleus, occasionally resulting in tumor regression.⁷³ Preclinical data showed that anti-EGFR therapies might inhibit tumor growth and proliferation, inducing tumor cell apoptosis. In addition, EGFR blockage enhances the effectiveness of current cytotoxic agents.⁷⁴⁻⁷⁶ Cetuximab (C225) and ABX-EGF, among other antibodies targeting EGFR, have been tested in metastatic CRC.

The ABX-EGF is a human IgG2 monoclonal antibody specific to human EGFR. The administration of ABX-EGF without concomitant chemotherapy was shown to be active.⁷⁷ Ongoing phase II trials are testing ABX-EGF in metastatic CRC, either alone or in combination with CPT-11, LV, and 5-FU.

Cetuximab (C225) is a chimeric human-murine IgG1 monoclonal antibody that binds selectively to EGFR. C225 induces apoptosis in different cancer cell lines and partially suppresses angiogenesis by inhibiting the production of vascular endothelial growth factor. Preclinical studies have also shown enhanced anti-tumor activity of chemotherapeutic agents by C225.^{78,79}

Phase II studies with C225 have shown activity in either chemotherapy-naive or previously treated metastatic CRC (Table 10).⁸⁰⁻⁸² Saltz et al⁸⁰ studied 121 patients with CRC refractory to 5-FU and CPT-11. These patients received a combination of C225 and CPT-11. The most common toxicity associated to IMC-C225 was acne-like skin rash/folliculitis grade 1 and 2 in 53% of patients. Toxicities of CPT-11 did not appear to be increased by C225. The RR determined by an independent review board was 22.5%, and the combination was considered active. In a subsequent phase II trial in 57 patients with CRC refractory to 5-FU and CPT-11, single-

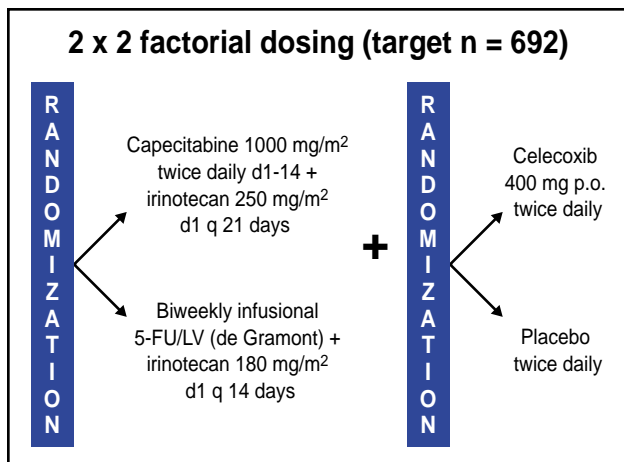


Fig 4. — Planned randomized phase III trial in metastatic CRC (EORTC 40015). Used with permission from the EORTC Gastrointestinal Group.

agent C225 resulted in a partial response in 6 patients (11%).⁸¹ The median survival had not yet been reached. In a recent report by Rosenberg et al,⁸² C225 in combination with IFL on the Saltz schedule as first-line treatment for EGFR-positive metastatic CRC resulted in an RR of 44%. No survival data have been reported. Surprisingly, when intensity of EGFR was tested, no correlation between response and the level (1+ to 3+) of EGFR expression was observed. Phase III trials incorporating C225 to standard chemotherapy drugs in CRC patients are ongoing or planned.

EGFR tyrosine kinase inhibitors reduce EGFR phosphorylation, leading to cell cycle arrest and apoptosis of cells expressing EGFR. ZD1839 (Iressa) is a potent oral anilinoquinazoline inhibitor of EGFR tyrosine kinase that blocks EGF-induced growth of tumor cells in culture. The drug has been tested in patients with solid tumors known to express or overexpress EGFR.⁸³ The most common adverse events were diarrhea and acne-like skin rash. Antitumor activity was most evident among non-small-cell lung cancer patients.⁸³

Preclinical studies have shown an enhanced growth inhibitory effect of ZD1839 combined with several chemotherapeutic agents that are active in CRC including raltitrexed, CPT-11, and oxaliplatin. In a pre-clinical model, inhibiting EGFR-TK activation with ZD1839 reversed resistance to SN-38 (an active metabolite of CPT-11) in human colon cancer cells.⁸⁴ In this study, the effect of ZD1839 on cellular determinants of resistance to SN-38 in drug-sensitive (HCT-8/wt) and drug-resistant (HCT-8/SN-38) human colon cancer cells was investigated. Coadministration of ZD1839 at noncytotoxic concentrations restored sensitivity to SN-38 in EGFR-expressing HCT-8/SN-38 cells. In addition, ZD1839 did not affect topo I, topo IIb, or general protein expression, but a significant time- and dose-dependent downregulation of topo IIa protein

and inhibition of its enzymatic function were observed.⁸⁴ To our knowledge, no phase II data with EGFR tyrosine kinase inhibitors in combination with chemotherapy in metastatic CRC have been reported.

OSI-774 (Tarceva) is another oral EGFR inhibitor that has been investigated in CRC. OSI-774 at 150 mg given orally daily in 16 metastatic CRC patients previously treated with Irinotecan and 5-FU given either in combination or sequentially has been reported in abstract form.⁸⁵ The preliminary efficacy results were disappointing since none of the 13 evaluable patients had a radiologic response. A number of other strategies targeting the EGFR pathway in CRC are being developed.⁸⁶

COX-2 Inhibitors

Cyclooxygenase (COX) is an enzyme that catalyses the synthesis of prostaglandins. COX-1 and COX-2 are the two isoforms, inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs).⁸⁷ COX-1 is constitutively expressed in a number of cell types, whereas COX-2 is an inducible enzyme whose expression and activity are up-regulated in response to a variety of cytokines, growth factors, and tumor promoters.^{88,89} Cyclooxygenase 2 (COX-2) is overexpressed in 71% to 85% of CRCs.^{88,90} Two potent COX-2 inhibitors, celecoxib and rofecoxib, are undergoing intense testing in different types of cancers including CRC.

Celecoxib has been further studied in patients with CRC. Blanke et al⁹¹ recently reported a phase II trial combining celecoxib with IFL in patients with untreated advanced CRC. A disappointing 28% partial RR in a group of 18 evaluable patients was observed. Lin et al⁹² reported a retrospective analysis of 67 patients taking either capecitabine and celecoxib or capecitabine alone as first- or second-line treatment of CRC. In this small retrospective study, celecoxib appeared to attenuate capecitabine-induced hand-foot syndrome, and the efficacy results suggested an improved TTP. Randomized trials in CRC are planned or underway to investigate the addition of celecoxib to either XELIRI or FOLFIRI regimens^{53,54} (Figs 3 and 4).

Farnesyltransferase Inhibitors

Farnesyltransferase is an enzyme that transfers farnesyl isoprenoid to proteins associated with cell membranes. Farnesyltransferase inhibitors (FTIs), which were developed as a strategy to attack Ras-dependent cancers, can inhibit malignant cell growth and tumor formation. Secretion of VEGF, synthesized by

many tumors, can be partially suppressed by FTIs. As a single-agent therapy, FTIs may be efficacious against premalignant lesions and may have the capability to block the growth of micrometastasis after primary site therapy. In addition, FTIs can potentially function as radiosensitizers and chemotherapy-enhancing agents.⁹³ A randomized trial with the FTI R115777 (Zarnestra) compared to placebo in 368 patients with previously treated metastatic CRC showed disappointing results.⁹⁴ The overall survival was not statistically different (5.7 months for the FTI arm and 6.1 months for the placebo arm). The signal transduction cascades are complex, and the relative importance of Ras is unclear.

Biological Markers

The development of predictive markers for response and survival in patients with CRC is essential. Despite improvements in the management of this disease, approximately half of patients with metastatic disease will receive chemotherapy and never achieve a response. In addition, selection of the appropriate chemotherapy regimen in the neoadjuvant setting may prove fruitful in “downstaging” patients with borderline resectable or unresectable CRC. In the adjuvant setting, the benefit of chemotherapy has been defined in patients with stage III (Dukes’ stage C) disease but is still debatable in patients with stage II disease. Predictive markers that direct the selection of the correct chemotherapy regimen and appropriate patient population to be treated in the adjuvant setting would help to identify patients who would benefit from adjuvant therapy. Thymidylate synthase, thymidine phosphorylase, dihydropyrimidine dehydrogenase, and microsatellite instability are among the markers being explored.

Thymidylate synthase (TS) catalyzes the conversion of 2-deoxyuridine 5-monophosphate and 5–10-methylene tetrahydrofolate to deoxythymidine monophosphate.⁹⁵ Insufficient TS inhibition may represent a major mechanism for fluoropyrimidines and other folate inhibitors resistance.^{96–98} In the setting of advanced metastatic disease, high levels of both TS mRNA and TS protein in malignant tissue from the metastatic disease site predict poor response to fluoropyrimidine-based therapy.^{96,99,100} However, TS levels at the primary tumor site do not appear to correlate with RR or survival in patients with metastatic disease.¹⁰¹

Thymidine phosphorylase (TP) catalyzes the reversible phosphorylation of thymidine to thymine, and it promotes transformation of pyrimidine antimetabolite drugs to active cytotoxic metabolites. Cellular deficiency of TP correlates with relative resis-

tance to 5-FU. Levels of TP are higher in tumor cells than in normal tissue. Elevated TP has been associated with advanced tumors.¹⁰²

DPD is a rate-limiting enzyme in the degradation pathway for 5-FU. The level of intratumoral DPD is an important co-determinant of tumor responsiveness to fluoropyrimidines therapy and is inversely proportional to survival.¹⁰³

Tumors characterized with high-frequency microsatellite instability (MSI-H) have alterations of repetitive nucleotide sequences in their DNA secondary to defective mismatch repair. MSI-H tumors are associated with a less aggressive clinical course and better prognosis than MSI-L (low-frequency) or MSS (microsatellite-stable) tumors.¹⁰⁴ Approximately 85% of colorectal cancers have normal DNA mismatch repair function and 15% exhibit MSI, with defective mismatch repair.¹⁰⁴ Studies suggested that MSI colon cancers have a much lower incidence of mutations in the *K-ras* oncogene and the p53 tumor suppressor gene than non-MSI colon cancers.¹⁰⁴ There is a potential for different susceptibilities to chemotherapeutic agents in MSS vs MSI-H tumors, and DNA mismatch repair-deficient cells appear to be resistant to 5-FU and topoisomerase inhibitors.¹⁰⁵

A better understanding of these prognostic and predictive markers is of great interest. However, at the time of this writing, the data are currently insufficient to allow the incorporation of these tests in the clinical practice and treatment decisions.

Conclusions

Advances in the treatment of metastatic CRC in the last decade have led to the development of more convenient drugs (oral fluoropyrimidines) and more effective regimens (CPT-11 or oxaliplatin added to fluoropyrimidines).

It is unlikely that classic cytotoxic drugs will produce additional improvements in the efficacy results. Several trials incorporating the newer molecular targeting drugs are underway. Improvement in the understanding of the biology of CRC may result in better targets or cellular pathways to be modified or blocked by therapeutic interventions. Additionally, improvements in the design of clinical trials and the incorporation of molecular surrogates into clinical research will lead to the development of better treatments. In the future, randomized studies should include quality of life and clinical economic components to justify potential minor therapeutic advances in relation to costly forms of treatment.

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