REVIEW ARTICLE

DRUG THERAPY

Systemic Therapy for Colorectal Cancer

Jeffrey A. Meyerhardt, M.D., M.P.H., and Robert J. Mayer, M.D.

From the Department of Medical Oncology, Dana–Farber Cancer Institute; the Department of Medicine, Brigham and Women's Hospital; and the Department of Medicine, Harvard Medical School — all in Boston. Address reprint requests to Dr. Meyerhardt at the Dana–Farber Cancer Institute, 44 Binney St., Boston, MA 02115.

N Engl J Med 2005;352:476-87.

Colorectal cancer is the third most common malignant disease and the second most frequent cause of cancer-related death in the United States, with 145,290 new cases and 56,290 deaths anticipated in 2005.[1] Worldwide, colorectal cancer is the fourth most commonly diagnosed malignant disease, with an estimated 1,023,000 new cases and 529,000 deaths each year.[2]

When the role of systemic treatment for colorectal cancer was last reviewed in the *Journal*, in 1994,[3] fluorouracil was the only effective chemotherapeutic drug for this cancer; much exciting progress has occurred since then. Accordingly, in this review, we will consider newer cytotoxic chemotherapies and biologic agents effective against colorectal cancer (Table 1) and will assess their uses for the treatment of metastatic disease and as components of adjuvant therapy. A discussion of combined therapeutic approaches (surgery, chemotherapy, and radiation) for patients with rectal cancer[5] is outside the scope of this review.

STAGING AND OTHER PROGNOSTIC INDICATORS

Pathological stage at the time of presentation remains the most important prognostic indicator in colorectal cancer. Although the original Dukes' staging system[6] has been modified, the depth of disease invasion through the bowel wall and the extent of regional lymph-node involvement remain the core of the staging system. The tumor–node–metastasis (TNM) system of the American Joint Committee on Cancer is now the most commonly used system for staging colorectal cancer and serves as a benchmark for predicting the likelihood of five-year survival (Table 2).[7]

Prospective studies have demonstrated that the use of chemotherapy in patients with metastatic disease prolongs survival and enhances quality of life in comparison to palliative care alone.[8-11] A meta-analysis of 13 such trials revealed that systemic chemotherapy led to an improvement in 1-year survival from 34 percent to 50 percent and an improvement in median survival by 3.7 months.[12]

FLUOROPYRIMIDINES

MECHANISMS OF ACTION AND DOSE SCHEDULING OF FLUOROURACIL

The backbone of treatment for colorectal cancer is fluorouracil, a fluorinated pyrimidine, which is thought to act primarily by inhibiting thymidylate synthase, the rate-limiting enzyme in pyrimidine nucleotide synthesis.[13] Fluorouracil is usually administered with leucovorin, a reduced folate, which stabilizes the binding of fluorouracil to thymidylate synthase, thereby enhancing the inhibition of DNA synthesis.[14] In patients with advanced colorectal cancer, treatment with fluorouracil and leucovorin reduces tumor size by 50 percent or more in approximately 20 percent of patients (the "objective-response rate") and prolongs median survival from approximately 6 months (without treatment) to about 11 months.[8-11,15]

The major side effects associated with fluorouracil depend on the method of administration. When the drug is given according to a "loading" schedule of bolus treatments on five consecutive days every four to five weeks, neutropenia and stomatitis are the most common toxic effects. In contrast, with weekly bolus doses, diarrhea is more frequent. Regimens involving fluorouracil administered as a continuous intravenous infusion (with a portable infusion pump) are associated with less hematologic and gastrointestinal toxicity, but palmar–plantar erythrodysesthesia ("hand–foot syndrome") is more common.[16-18] Although regimens involving continuous intravenous infusion were previously perceived as being more expensive and less convenient than bolus regimens, recent analyses suggest that differences in cost and quality of life between the bolus and prolonged-infusion schedules are marginal.[19-21] Furthermore, continuous infusion appears to be moderately more effective than a rapid bolus approach.[22]

Table 1. Glossary of Treatments for Colorectal Cancer.*

FDA-approved drugs
Fluorouracil
Capecitabine (Xeloda)
Irinotecan (Camptosar)
Oxaliplatin (Eloxatin)
Cetuximab (Erbitux)
Bevacizumab (Avastin)

FDA-approved combination regimens
IFL: Irinotecan, bolus fluorouracil, and leucovorin — first-line therapy
FOLFIRI: Irinotecan, infusional fluorouracil, and leucovorin — first-line therapy†
FOLFOX: Oxaliplatin, infusional fluorouracil, and leucovorin — first- and second-line therapy
Intravenous fluorouracil and bevacizumab — first-line therapy
Cetuximab and irinotecan — therapy for EGFR-positive,‡ irinotecan-refractory disease

* FDA denotes Food and Drug Administration, and EGFR epidermal growth factor receptor.
† FOLFIRI, as described by Douillard et al.,[4] is the more commonly used variation of another combination of infusional fluorouracil, leucovorin, and irinotecan approved by the FDA.
‡ Immunohistochemistry testing is used to determine EGFR status.

ORAL FLUOROPYRIMIDINES

Early attempts to administer fluorouracil orally fell into disfavor after the results of a double-blind, placebo-controlled, randomized study showed intravenous fluorouracil to be more effective than the oral form.[23] Pharmacokinetic plasma assays suggested that this discrepancy was due to the erratic intestinal absorption of oral fluorouracil, which may in turn have been a result of the variable mucosal concentrations of dihydropyrimidine dehydrogenase, a major catabolic enzyme of the drug. Strategies developed to overcome this problem include the administration of fluorouracil prodrugs that are absorbed intact and metabolically activated after intestinal absorption[24] and the coadministration of oral fluorouracil with drugs that inhibit the action of dihydropyrimidine dehydrogenase.[25-27]

Capecitabine (Xeloda) is a prodrug that undergoes a three-step enzymatic conversion to fluorouracil.[24] The side-effect profile of capecitabine is similar to that observed when fluorouracil is given as a protracted infusion. The hand–foot syndrome is a prominent toxic effect; other adverse reactions include diarrhea, nausea, vomiting, and bone marrow suppression.[28-30] Two randomized clinical trials comparing capecitabine to the monthly schedule of fluorouracil and leucovorin[28,29] reported that the rate of objective response in patients treated with capecitabine was moderately improved (19 to 25 percent, as compared with 15 percent); median overall survival, however, was similar between the two regimens (12 to 13 months). Mouth sores and bone marrow suppression were more likely to develop in patients receiving a loading regimen of intravenous fluorouracil, whereas patients assigned to receive capecitabine had an increased incidence of the hand–foot syndrome.

An example of an oral fluorouracil combination that inhibits dihydropyrimidine dehydrogenase is uracil plus tegafur, which has been approved by regulatory agencies outside the United States. Tegafur, a prodrug of fluorouracil, is combined with uracil, which is a competitive blocker of dihydropyrimidine dehydrogenase, to improve the absorption and bioavailability of tegafur.[26] The combination is usually administered with oral leucovorin. In two randomized studies, this therapy resulted in a response rate and median overall survival similar to those obtained with parenteral fluorouracil and leucovorin.[31,32]

As monotherapy, the oral fluoropyrimidines appear to have favorable safety, convenience, and cost-effectiveness profiles when compared with bolus intravenous fluorouracil administered on five consecutive days every four to five weeks.[33] Whether such benefits would remain if the oral agents were

Table 2. TNM Staging System for Colorectal Cancer. *

Stage	TNM Classification	Five-Year Survival
		%
I	T1–2, N0, M0	>90
IIA	T3, N0, M0	60–85
IIB	T4, N0, M0	
IIIA	T1–2, N1, M0	25–65
IIIB	T3–4, N1, M0	
IIIC	T (any), N2, M0	
IV	T (any), N (any), M1	5–7

Primary tumor (T)

TX: Primary tumor cannot be assessed

Tis: Carcinoma in situ

T1: Tumor invades submucosa

T2: Tumor invades muscularis propria

T3: Tumor penetrates muscularis propria and invades subserosa

T4: Tumor directly invades other organs or structures or perforates visceral peritoneum

Nodal status (N)

NX: Regional lymph nodes cannot be assessed

N0: No metastases in regional lymph nodes

N1: Metastases in one to three regional lymph nodes

N2: Metastases in four or more regional lymph nodes

Distant metastases (M)

MX: Presence or absence of distant metastases cannot be determined

M0: No distant metastases detected

M1: Distant metastases detected

* The information is from Greene et al.[7]

compared with a less toxic method of administering intravenous fluorouracil (e.g., as a weekly bolus) or if capecitabine were combined with parenteral chemotherapies remains to be determined.

ADJUVANT THERAPY WITH FLUOROURACIL

For many years, the use of fluorouracil as adjuvant treatment after complete resection of stage II cancers (T3 or T4 with negative lymph nodes, according to the TNM system) or stage III cancers (any T stage with positive lymph nodes) was thought to be ineffective.[34] In retrospect, previous randomized studies were limited both by insufficient numbers of patients as well as by suboptimal adherence to chemotherapy. Better-conducted randomized trials in patients with stage III disease showed that intravenous fluorouracil[35] or fluorouracil plus leucovorin[36-38] did improve outcomes. A pooled analysis of patients with stage III disease who were participating in seven clinical trials of adjuvant therapy demonstrated that adjuvant chemotherapy increased the probability of remaining free of tumor recurrence after five years from 42 percent to 58 percent and the likelihood of five-year overall survival from 51 percent to 64 percent.[39] Two recent randomized trials that compared either capecitabine or uracil plus tegafur to parenteral fluorouracil showed that oral and intravenous fluoropyrimidine therapies appear to offer equivalent efficacy.[40,41] Adjuvant therapy has been found to be as beneficial in elderly patients as it is in younger patients.[39,42]

The value of postoperative fluorouracil-based therapy after the resection of stage II colon cancers has remained controversial, however.[43-45] No randomized clinical trial has demonstrated a survival benefit for this group of patients, and an analysis of data pooled from seven such studies showed five-year survival probabilities in the range of 80 percent, with or without treatment.[39] An expert panel convened by the American Society of Clinical Oncology recently concluded that adjuvant chemotherapy should not be routinely recommended for all patients with stage II disease. According to the available data, the absolute survival advantage associated with such treatment could not exceed 5 percent, and the inclusion of at least 4000 patients would be required to detect a potentially smaller benefit.[46] A retrospective subgroup analysis[44] has suggested that patients with prognostic factors associated with increased rates of recurrence (e.g., adherence of the tumor to an adjacent organ or bowel perforation or obstruction) may benefit from adjuvant treatment; however, no prospective study has yet validated this observation. According to insurance-claims data, 30 percent of Medicare beneficiaries (i.e., Americans older than 65 years of age) with stage II disease receive such treatment.

REGIONAL THERAPY WITH FLUOROPYRIMIDINES

The rationale for administering chemotherapeutic agents directly into the liver in the presence of hepatic metastases is based on the dual blood supply of the liver: tumors derive most of their blood from the hepatic artery, while the portal circulation supplies the normal liver parenchyma. Infusions of fluorouracil or an analogue compound, floxuridine, into the hepatic artery results in a doubling of the

response rates achieved with systemic administration of fluorouracil. However, no survival advantage has been demonstrated for patients with more advanced disease, most often because of the presence of metastases outside the liver.[47] Furthermore, toxic effects that include chemical hepatitis, cholangitis, and catheter-related complications, as well as the high overall costs of this therapy, limit its practical value.[47-49]

To date, randomized studies assessing hepatic arterial infusion of fluorouracil or floxuridine as adjuvant therapy after the resection of liver metastases, as compared with either surgery alone[50,51] or systemic chemotherapy,[52] have failed to demonstrate an improvement in the likelihood of a cure with this type of adjuvant therapy, although one of these trials reported a significant difference in a predefined, two-year survival end point between hepatic infusion and systemic chemotherapy alone.[52]

IRINOTECAN

MECHANISMS OF ACTION AND TOXIC EFFECTS

Irinotecan (Camptosar, also known as CPT-11) is a semisynthetic derivative of the natural alkaloid camptothecin, which exerts a cytotoxic effect through its interaction with the enzyme topoisomerase I.[53] This enzyme is involved in the uncoiling of DNA for replication and transcription, and it causes single-stranded DNA breaks. Such breaks are normally transient and repaired; however, camptothecin stabilizes these breaks, leading to DNA fragmentation and cell death through interaction with the replication fork.

Irinotecan is a prodrug that is hydrolyzed to its active metabolite, SN-38, by hepatic carboxylesterases. SN-38 is detoxified to an inactive, glucuronidated form by uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1) and is excreted in the urine and bile.[54] Several additional inactive metabolites of irinotecan are formed through oxidative metabolism by the cytochrome P-450 enzymes CYP3A4 and CYP3A5.[55]

The toxic effects of irinotecan include diarrhea, bone marrow suppression, nausea, vomiting, and alopecia. Polymorphisms of UGT1A1 appear to correlate with the severity of the gastrointestinal effects and bone marrow suppression,[56-58] and clinical trials are currently under development to individualize drug dosages on the basis of a given patient's pharmacogenomic profile.

TREATMENT OF METASTATIC DISEASE WITH IRINOTECAN

Two randomized trials of single-agent irinotecan as a second-line therapy in patients with advanced colorectal cancer who had previously received bolus fluorouracil showed a two-to-three-month improvement in median overall survival as compared with either best supportive care alone[9] or fluorouracil given by continuous infusion,[59] accompanied by similar or improved quality of life. Irinotecan was subsequently examined in combination with fluorouracil and leucovorin as initial therapy for metastatic colorectal cancer; a bolus schedule (known as IFL) was tested in North America[60] and a 48-hour infusion program was tested in Europe.[4] Both of these multicenter trials indicated that the three-drug combination was twice as likely as fluorouracil and leucovorin alone to result in a 50 percent or greater shrinkage of tumor dimensions, resulting in a two-month extension in median survival.

Adding irinotecan to bolus fluorouracil and leucovorin increases the likelihood of clinically significant myelosuppression and diarrhea.[4,60] This toxicity pattern led to a higher-than-anticipated number of treatment-related deaths when the combination of irinotecan, fluorouracil, and leucovorin was first used[61]; however, prompt attention to and treatment of toxic effects as well as adjustments in dosing and scheduling of the regimen have rendered this combination more tolerable and safer.[61-63]

OXALIPLATIN

MECHANISMS OF ACTION AND TOXIC EFFECTS

Oxaliplatin (Eloxatin) is a third-generation platinum derivative that forms bulky DNA adducts and induces cellular apoptosis.[64] Despite the ineffectiveness of other platinum-based drugs (such as cisplatin and carboplatin) in the treatment of colorectal cancer, preclinical data from human cell lines suggested that oxaliplatin held promise in treating this disease.[65] Furthermore, oxaliplatin and fluorouracil were shown to be highly synergistic, not only in preclinical models[66] but also in subsequent clinical trials.[67] A potential mechanism for this synergy is the down-regulation of thymidylate synthase by oxaliplatin, which thereby potentiates the efficacy of fluorouracil.[68]

The toxicity profile of oxaliplatin differs from those of cisplatin and carboplatin. Renal dysfunction, alopecia, and ototoxic effects are uncommon,

but neuropathy is more frequent.[69] Two types of neuropathies have been described. Most patients experience transient dysesthesias, manifested as numbness or tingling of the hands and feet and the oral or perioral regions, which are exacerbated by exposure to low temperatures. After months of therapy, patients may have a cumulative, dose-dependent sensory neuropathy in which peripheral dysesthesias and paresthesias persist between cycles of therapy; these effects usually diminish after the cessation of treatment.[70]

TREATMENT OF METASTATIC DISEASE WITH OXALIPLATIN

Although oxaliplatin as a single agent has limited efficacy when administered as first-line[71-73] or second-line[74] treatment for patients with metastatic colorectal cancer, clinical benefit has been shown when it is combined with bolus fluorouracil and leucovorin followed by a 46-hour infusion of fluorouracil — a treatment regimen known as FOLFOX.[67,70,75,76] Randomized clinical trials have consistently shown that FOLFOX results in response rates and times to disease progression that are superior to those achieved with fluorouracil and leucovorin when given as first-line[70,75,76] or second-line[67] treatment for advanced colorectal cancer. There was a trend toward improvement in overall survival, but it did not reach statistical significance in these initial studies.

IS THERE AN OPTIMAL FIRST-LINE THERAPY FOR METASTATIC DISEASE?

Comparisons of irinotecan, fluorouracil, and leucovorin regimens with oxaliplatin, fluorouracil, and leucovorin combinations for the initial treatment of metastatic colorectal cancer have recently been reported (Table 3). In a multicenter trial conducted in North America, 795 patients were randomly assigned to receive IFL, FOLFOX, or a combination of irinotecan with oxaliplatin (IROX).[77] The patients treated with FOLFOX had a response rate, time to disease progression, and overall survival time that were superior to those observed with either IFL or IROX. However, the apparent superiority of FOLFOX may have been influenced by an imbalanced availability of second-line agents at the time the study was conducted in that 60 percent of the patients initially treated with FOLFOX subsequently received irinotecan, whereas only 24 percent in the IFL group were subsequently given oxaliplatin. In addition, the IFL regimen is based on a bolus-fluorouracil schedule that may be inferior to the two-day infusion of fluorouracil included in FOLFOX.[22] Nonetheless, these data support the option of oxaliplatin-based therapy as first-line combination therapy for patients with metastatic disease.

Two European trials with predefined crossover designs have further addressed this issue (Table 3). Tournigand and colleagues, whose randomized study included 220 patients, found that a regimen of infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) followed by FOLFOX yielded response rates and median overall survival times indistinguishable from those obtained with a regimen of FOLFOX followed by FOLFIRI.[78] In a similarly designed trial involving 161 patients, Grothey et al. found no appreciable differences in efficacy between capecitabine combined with irinotecan and capecitabine combined with oxaliplatin.[79] Definitive interpretation of these studies is limited by their small numbers of patients, yet the consistency of the results suggests equivalence between irinotecan-based regimens and oxaliplatin-based regimens when combined with comparable fluorouracil therapies.

Thus, the optimal sequence of these chemotherapy agents is currently unclear. The choice of initial therapy could depend on a given patient's coexisting conditions at baseline. For example, for patients who have an underlying neuropathy, irinotecan-based regimens may be more appropriate than oxaliplatin-based regimens, which may have neurotoxic effects, whereas for patients with underlying bowel dysfunction, oxaliplatin-based therapy may be more appropriate than irinotecan-based therapy, which may have toxic effects on the gastrointestinal system. Despite the choice of initial therapy, exposure to each of these cytotoxic agents at some time over the course of a patient's disease has been associated with prolonged survival.[80]

INCORPORATION OF OXALIPLATIN AND IRINOTECAN INTO ADJUVANT THERAPY

Attempts to integrate irinotecan and oxaliplatin into adjuvant-treatment programs have been the focus of at least four clinical trials. The initial results of two of these studies have been reported thus far.

Saltz and colleagues assigned 1264 patients with

Table 3. Comparative Trials of Irinotecan and Oxaliplatin as First-Line Therapy for Metastatic Colorectal Cancer.*

Trial and Regimens	No. of Patients	Rate of Response	P Value†	Median Time to Progression	P Value	Median Overall Survival	P Value†
		%		*mo*		*mo*	
Goldberg et al.[77]							
IFL	264	31		7.0		15.0	
FOLFOX	267	45	<0.001	9.3	0.002	19.5	<0.001
IROX	264	35	0.3	6.5	0.5	17.4	0.04
Tournigand et al.[78]‡							
FOLFIRI	109	56		8.5		21.5	
FOLFOX	111	54	NS	8.0	0.3	20.6	0.99
Grothey et al.[79]‡							
Irinotecan plus capecitabine	79	43		7.9		>16	
Oxaliplatin plus capecitabine	82	51	0.3	7.9	0.3	>16	NS

* This table includes the results of trials of first-line therapy only. IFL denotes irinotecan and bolus fluorouracil; FOLFOX oxaliplatin, infusional fluorouracil, and leucovorin; FOLFIRI irinotecan, infusional fluorouracil, and leucovorin; and NS not significant.

† P values are for the comparison with the IFL regimen (the control) in the trial reported by Goldberg et al.,[77] with the FOLFIRI regimen in the trial reported by Tournigand et al.,[78] and with the irinotecan and capecitabine regimen in the trial reported by Grothey et al.[79]

‡ In these studies, patients crossed over to the other group at the time of progression of disease or intolerance of first-line therapy.

stage III disease to receive either IFL or bolus fluorouracil and leucovorin. After a median follow-up period of 2.6 years, IFL therapy did not improve either the probability of recurrence or overall survival, but it significantly increased the risks of diarrhea and myelosuppression.[81] This unanticipated outcome emphasizes the need for caution in extrapolating positive results from the setting of metastatic disease to adjuvant treatment. The outcome of a European trial of infusional fluorouracil in combination with irinotecan has not yet been reported.

In contrast, the initial results of a European trial in which 2200 patients with stage II and stage III colon cancer were randomly assigned to receive either FOLFOX or infusional fluorouracil and leucovorin showed that the FOLFOX-treated cohort had a greater likelihood of remaining free of recurrence after four years (76 percent vs. 69 percent, P<0.001).[82,83] This difference was far more evident among patients with stage III disease (70 percent in the FOLFOX group vs. 61 percent in the fluorouracil-and-leucovorin group, P=0.002) than among those with stage II disease (85 percent vs. 81 percent, difference not significant). FOLFOX treatment has not yet been found to confer a statistically significant advantage in terms of overall survival. Peripheral neuropathy was the major side effect of the FOLFOX regimen, occurring in 92 percent of the patients and classified as grade 3 (i.e., limiting the activities of daily living) in 12 percent. The neurotoxic effects were generally reversible; 18 months after the completion of therapy, 76 percent of patients reported no neurologic impairment, and only 4 percent had residual grade 2 or 3 symptoms. These data have expanded the options for treating patients with early-stage disease; however, the risks and benefits of this more toxic regimen should be assessed in individual patients.

TARGETED THERAPIES

Laboratory studies have identified molecular sites in tumor tissue that may serve as specific targets for treatment. The goal of such a therapeutic strategy is the interruption of cellular pathways essential for tumor growth, survival, and metastasis and, potentially, a reduction in the toxic effects associated with less specific cytotoxic chemotherapies.

Currently, two promising classes of targeted compounds have been introduced into the clinical management of advanced colorectal cancer: epidermal growth factor receptor antagonists and angiogenesis inhibitors.

CETUXIMAB

The epidermal growth factor receptor is a transmembrane glycoprotein that is involved in signaling pathways affecting cellular growth, differentiation, proliferation, and programmed cell death.[84] The receptor is present on the surface of normal epithelium and is overexpressed in certain tumors. Such overexpression has been associated with a poorer prognosis in colorectal cancer.[85,86] Inhibition of this target can be achieved by antibodies directed against the extracellular domain or the soluble ligands of the receptor, inhibitors of the required dimerization of the receptor, or small molecules that prevent phosphorylation of the receptor by its intracellular tyrosine kinase. Cetuximab (Erbitux, also known as C-225) is a monoclonal antibody against the extracellular binding domain of the receptor and recently became the first such inhibitor to be approved in the United States for the treatment of metastatic colorectal cancer.

Preclinical studies have shown not only that therapeutic synergy exists between cetuximab and chemotherapeutic agents, but also that such synergy can occur in tumor cells already resistant to irinotecan — a finding suggesting that the inhibitor may overcome cellular resistance to irinotecan.[87] As such, Saltz and colleagues gave a combination of cetuximab and irinotecan to 121 patients with advanced colorectal cancer whose tumor had been found to be unresponsive to irinotecan; 19 percent of the patients had radiographically objective tumor shrinkage[88] (Table 4). To determine whether this antitumor effect was due to synergy between the two drugs or due to the independent activity of cetuximab, 60 similar patients were treated with the antibody alone; 10 percent of them had radiographically significant tumor regression.[89]

These experiences were confirmed and extended by Cunningham and colleagues, who randomly assigned 329 patients with advanced colorectal cancer that was refractory to irinotecan to receive either cetuximab with irinotecan or cetuximab alone (Table 4).[90] This larger clinical trial resulted in an almost identical, 23 percent rate of disease regression in patients given the combination and 11 percent in those who received single-agent cetuximab.

The side effects of cetuximab are fairly mild, with an acne-like rash and drying and fissuring of the skin the most common; hypersensitivity infusion reactions are less frequent (occurring in 3 percent of patients, with death in fewer than 1 in 1000). Although some degree of acneiform rash occurs in most patients, severe eruptions resulting in significant pain, pruritus, or infectious sequelae are rare. Of note, the development and severity of the rash have been correlated with an increased likelihood of an objective response; the mechanism underlying this correlation is currently unclear.[94]

These data suggest that cetuximab is effective in a subgroup of patients with advanced colorectal cancer. The trials reported to date have included only patients with immunohistochemical evidence of epidermal growth factor receptor expression. However, the degree of such expression appears to be unrelated to the likelihood of disease regression,[90] raising questions as to whether receptor overexpression should be a prerequisite for cetuximab treatment and whether the drug is interacting with additional molecular targets.

BEVACIZUMAB

The appreciation that tumors induce blood-vessel formation, allowing extension beyond a few millimeters in size, stimulated efforts at inhibiting this type of angiogenesis as a means of controlling the growth and spread of cancer cells.[95] The most successful of these efforts to date has focused on neutralizing the vascular endothelial growth factor, which is a soluble protein instrumental in angiogenesis.[96] Bevacizumab (Avastin), a humanized antibody directed against the vascular endothelial growth factor, has been examined in combination with chemotherapeutic agents in several clinical trials in patients with advanced colorectal cancer (Table 4).[91,93,97] A small, randomized, phase 2 trial in patients who had received no prior treatment for their metastatic disease showed that bevacizumab, as compared with fluorouracil and leucovorin alone, improved the likelihood of a tumor response.[91] This effort led to two concurrent randomized, phase 3 trials.

Hurwitz and colleagues assigned 815 patients to receive either IFL with bevacizumab or IFL with placebo.[93] The addition of bevacizumab led to an impressive, statistically significant increase in the rate of response and a 4.7-month prolongation in median overall survival (to 20.3 months, vs. 15.6 months with IFL and placebo). In a study involving

Table 4. Trials of Targeted Therapies in Metastatic Colorectal Cancer.*

Trial and Regimen	Type of Study	No. of Patients	Rate of Response	Median Time to Progression	Median Overall Survival
			%	*mo*	*mo*
Cetuximab					
Saltz et al.[88]: cetuximab and irinotecan	Phase 2	121	19	NR	NR
Saltz et al.[89]: cetuximab only	Phase 2	57	11	1.4	6.4
Cunningham et al.[90]	Randomized, phase 2				
Cetuximab only†		111	11	1.5	6.9
Cetuximab and irinotecan		218	23	4.1	8.6
Bevacizumab					
Kabbinavar et al.[91]	Randomized, phase 2				
Fluorouracil and leucovorin		36	17	5.2	13.8
Fluorouracil, leucovorin, and bevacizumab		68	32	7.4	16.1 and 21.5‡
Kabbinavar et al.[92]	Phase 3				
Fluorouracil and leucovorin		105	15	5.5	12.9
Fluorouracil, leucovorin, and bevacizumab		104	26 (P=0.06)	9.2 (P<0.001)	16.6 (P=0.16)
Hurwitz et al.[93]	Phase 3				
IFL		412	35	6.2	15.6
IFL and bevacizumab		403	45 (P=0.004)	10.6 (P<0.001)	20.3 (P<0.001)

* NR denotes not reported, and IFL irinotecan, fluorouracil, and leucovorin.
† Patients in the cetuximab-only group were allowed to cross over to the cetuximab-and-irinotecan group on progression of disease. Fifty-four of the patients who initially were randomly assigned to single-agent cetuximab crossed over, with 3.6 percent having a partial response and 35.7 percent having stable disease.
‡ In this trial, two groups received bevacizumab: one group received 10 mg per kilogram of body weight and had a median overall survival of 16.1 months, and the other group received 5 mg per kilogram and had a median overall survival of 21.5 months.

patients considered unable to tolerate irinotecan, Kabbinavar et al.[92] found that bevacizumab added to fluorouracil and leucovorin improved response rates and extended the time to tumor progression but did not significantly prolong median survival. In both studies,[92,93] bevacizumab was associated with reversible hypertension and proteinuria and was relatively well tolerated. Recently, a statistically significant prolongation in median survival was reported with the addition of bevacizumab to FOLFOX, as compared with FOLFOX alone, in patients with advanced colorectal cancer who had previously been treated with irinotecan-based therapy.[98]

The Food and Drug Administration approved the use of bevacizumab in combination with any intravenous fluorouracil-containing regimen as initial therapy for patients with advanced colorectal cancer. Although the addition of this drug clearly represents a therapeutic advance against this disease, further studies are required to define the extent of its clinical usefulness. Bevacizumab appears to be inactive as a single agent, and its efficacy when added to nonintravenous fluorouracil regimens is currently unknown. It is also unclear whether its activity is generated primarily by an antiangiogenic mechanism or whether it exerts its effect by altering tumor vasculature, thereby enhancing the intracellular access of chemotherapeutic agents.[93,99]

FUTURE DIRECTIONS AND CHALLENGES

The recent introduction of cytotoxic drugs in addition to fluorouracil as well as the development of targeted agents has resulted in significant progress in the treatment of advanced colorectal cancer. Whereas the median life expectancy for people with this condition is in the range of 6 months without the use of any form of treatment and is extended to 10 to 12 months when either fluorouracil alone or

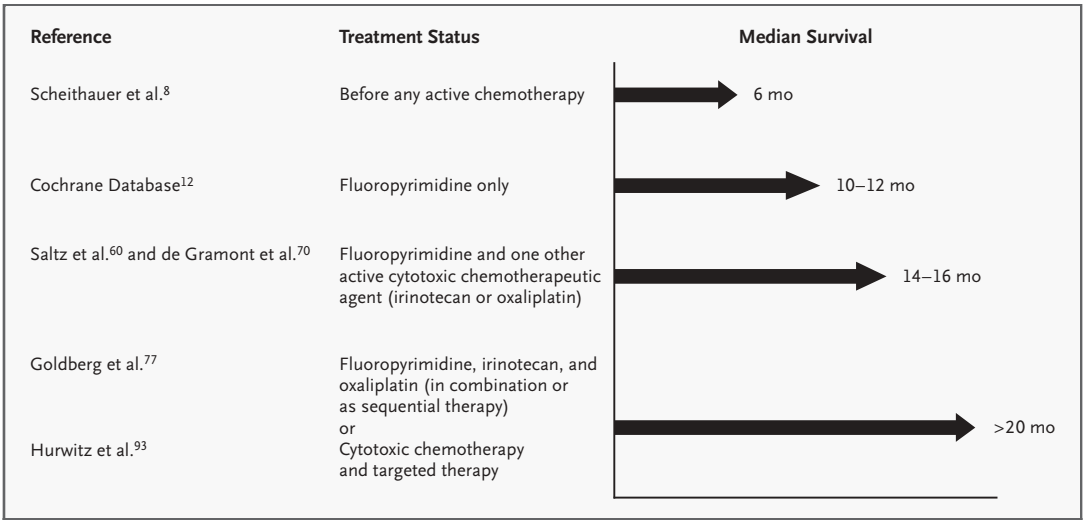

Figure 1. Trends in the Median Survival of Patients with Advanced Colorectal Cancer.
Adapted from Grothey et al.[80]

fluorouracil combined with leucovorin is administered, the median survival is increased to 14 to 16 months when either irinotecan or oxaliplatin is added to a fluorouracil-based treatment regimen. Survival appears to be further prolonged, to more than 20 months, when all three drugs are used at some point in the care of the patient or if a form of targeted therapy (e.g., bevacizumab) is combined with a cytotoxic-drug combination (Fig. 1). Data suggest that the introduction of at least some of these combination regimens, when administered as adjuvant treatment after surgery,[82,83] may further enhance the likelihood of cure.

How best to incorporate these potent new therapeutic tools into treatment plans for individual patients remains to be determined. The rapid approval of multiple active agents has made it difficult to design and complete the clinical trials necessary to provide this information. Consequently, physicians have been left with uncertainty as to which form of treatment to use first and how best to combine these different types of therapy.

Efforts are under way, however, to develop ways in which therapy can be tailored for individual patients. Intratumoral levels of various enzymes involved in fluorouracil activation and metabolism, such as thymidylate synthase, dihydropyrimidine dehydrogenase, and thymidine phosphorylase, have been examined to identify patients with advanced colorectal cancer who are likely to benefit from fluorouracil treatment. Unfortunately, these studies have yielded conflicting outcomes.[100-105] The efficacy and toxicity of specific drugs in individual patients will be more readily assessable once the genetic polymorphisms and mutations affecting the metabolic pathways of various chemotherapeutic agents as well as the biologic pathways of targeted agents have been fully studied.[106,107]

Substantial progress is being made in the identification of new forms of treatment for colorectal cancer. Patients with metastatic disease are living twice as long as they were one decade ago. The use of adjuvant chemotherapy has increased the likelihood of cure by 30 percent among patients with stage III disease. In 1994, Moertel concluded his review of chemotherapy for colorectal cancer by noting that "these [new] treatments will stimulate continued research in the treatment of colorectal cancer."[3] The same statement can be made today. Unresectable, advanced colorectal cancer remains incurable. As in the past, further progress can take place only through the completion of well-designed, randomized clinical trials.

Supported in part by a K07 award from the National Cancer Institute (1K07CA097992-01A1, to Dr. Meyerhardt) and an American Society of Clinical Oncology career development award.

Dr. Meyerhardt reports having received a consulting fee from Bristol-Myers Squibb and a lecture fee and grant support from Sanofi-Synthelabo and reports having given lectures as part of speakers'

bureaus (Thompson Professional, which is supported by Pfizer; Health Sciences, which is supported by Sanofi-Synthelabo; and Health Sciences, which is supported by Genentech). He is the lead investigator in a multidrug trial involving capecitabine (Roche), oxaliplatin (Sanofi-Synthelabo), and erlotinib (Genentech) but does not receive salary support for this work. Dr. Mayer reports having received a consulting fee from Pfizer.

We are indebted to Drs. Charles S. Fuchs and Matthew H. Kulke for their critical review of the manuscript.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10-30.
2. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase no. 5, version 2.0. Lyon, France: IARC Press, 2004.
3. Moertel CG. Chemotherapy for colorectal cancer. N Engl J Med 1994;330:1136-42.
4. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355:1041-7. [Erratum, Lancet 2000;355:1372.]
5. Minsky BD. Adjuvant therapy of resectable rectal cancer. Cancer Treat Rev 2002;28:181-8.
6. Dukes CE. The classification of cancer of the rectum. J Pathol 1932;35:323-32.
7. Greene FL, Balch CM, Fleming ID, et al., eds. AJCC cancer staging handbook. 6th ed. New York: Springer, 2002.
8. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ 1993;306:752-5.
9. Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1413-8.
10. Smyth JF, Hardcastle JD, Denton G, et al. Two phase III trials of tauromustine (TCNU) in advanced colorectal cancer. Ann Oncol 1995;6:948-9.
11. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. Lancet 1994;344:1255-60.
12. Palliative chemotherapy for advanced or metastatic colorectal cancer: Colorectal Meta-analysis Collaboration. Cochrane Database Syst Rev 2000;2:CD001545.
13. Sobrero A, Guglielmi A, Grossi F, Puglisi F, Aschele C. Mechanism of action of fluoropyrimidines: relevance to the new developments in colorectal cancer chemotherapy. Semin Oncol 2000;27:Suppl 10:72-7.
14. Zhang ZG, Harstrick A, Rustum YM. Modulation of fluoropyrimidines: role of dose and schedule of leucovorin administration. Semin Oncol 1992;19:Suppl 3:10-5.
15. Thirion P, Michiels S, Pignon JP, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. J Clin Oncol 2004;22:3766-75.
16. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program study. J Clin Oncol 1989;7:425-32.
17. de Gramont A, Bosset JF, Milan C, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 1997;15:808-15.
18. Weh HJ, Wilke HJ, Dierlamm J, et al. Weekly therapy with folinic acid (FA) and high-dose 5-fluorouracil (5-FU) 24-hour infusion in pretreated patients with metastatic colorectal carcinoma: a multicenter study by the Association of Medical Oncology of the German Cancer Society (AIO). Ann Oncol 1994;5:233-7.
19. Lokich JJ, Moore CL, Anderson NR. Comparison of costs for infusion versus bolus chemotherapy administration — part two: use of charges versus reimbursement for cost basis. Cancer 1996;78:300-3.
20. *Idem*. Comparison of costs for infusion versus bolus chemotherapy administration: analysis of five standard chemotherapy regimens in three common tumors. 1. Model projections for cost based on charges. Cancer 1996;78:294-9.
21. Köhne CH, Wils J, Lorenz M, et al. Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer: European Organization of Research and Treatment of Cancer Gastrointestinal Group Study 40952. J Clin Oncol 2003;21:3721-8.
22. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998;16:301-8.
23. Hahn RG, Moertel CG, Schutt AJ, Bruckner HW. A double-blind comparison of intensive course 5-fluorouracil by oral vs. intravenous route in the treatment of colorectal carcinoma. Cancer 1975;35:1031-5.
24. Pentheroudakis G, Twelves C. The rational development of capecitabine from the laboratory to the clinic. Anticancer Res 2002;22:3589-96.
25. Meropol NJ. Oral fluoropyrimidines in the treatment of colorectal cancer. Eur J Cancer 1998;34:1509-13.
26. Sulkes A, Benner SE, Canetta RM. Uracil-ftorafur: an oral fluoropyrimidine active in colorectal cancer. J Clin Oncol 1998;16:3461-75.
27. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 1998;34:1715-20.
28. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097-106.
29. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19:2282-92.
30. Mayer RJ. Oral versus intravenous fluoropyrimidines for advanced colorectal cancer: by either route, it's all the same. J Clin Oncol 2001;19:4093-6.
31. Carmichael J, Popiela T, Radstone D, et al. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3617-27.
32. Douillard JY, Hoff PM, Skillings JR, et al. Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3605-16.
33. Ward S, Kaltenthaler E, Cowan J, Brewer N. Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation. Health Technol Assess 2003;7:1-93.
34. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer: why we still don't know. JAMA 1988;259:3571-8.
35. Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med 1995;122:321-6.
36. Haller DG, Lefkopoulou M, Macdonald JS, Mayer RJ. Some considerations concern-

ing the dose and schedule of 5FU and leucovorin: toxicities of two dose schedules from the intergroup colon adjuvant trial (INT-0089). Adv Exp Med Biol 1993;339:51-6.
37. Haller DG, Catalano PJ, Macdonald JS, Mayer RJ. Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: five-year final report of INT-0089. Proc Am Soc Clin Oncol 1998;17:982. abstract.
38. Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. J Clin Oncol 1999;17:3553-9.
39. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797-806.
40. Wolmark N, Wieand S, Lembersky B, Colangelo L, Smith R, Pazdur R. A phase III trial comparing oral UFT in stage II and III carcinoma of the colon: results of NSABP protocol C06. J Clin Oncol 2004;22:Suppl: 3508. abstract.
41. Cassidy J, Scheithauer W, McKendrick J, et al. Capecitabine vs bolus 5-FU/leucovorin as adjuvant therapy for colon cancer (the X-ACT study): positive efficacy results of a phase III trial. J Clin Oncol 2004;22:Suppl: 3509. abstract..
42. Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001;345:1091-7.
43. Mamounas E, Wieand S, Wolmark N, et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04). J Clin Oncol 1999;17:1349-55.
44. Moertel CG, Fleming TR, Macdonald JS, et al. Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes' B2 colon cancer. J Clin Oncol 1995; 13:2936-43.
45. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. J Clin Oncol 1999;17:1356-63.
46. Benson AB III, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408-19.
47. Meta-Analysis Group in Cancer. Re-appraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst 1996;88:252-8.
48. Durand-Zaleski I, Earlam S, Fordy C, Davies M, Allen-Mersh TG. Cost-effectiveness of systemic and regional chemotherapy for the treatment of patients with unresectable colorectal liver metastases. Cancer 1998; 83:882-8.
49. Barnett KT, Malafa MP. Complications of hepatic artery infusion: a review of 4580 reported cases. Int J Gastrointest Cancer 2001;30:147-60.
50. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy — an intergroup study. J Clin Oncol 2002;20:1499-505.
51. Lorenz M, Muller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. Ann Surg 1998;228:756-62.
52. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 1999;341: 2039-48.
53. Iyer L, Ratain MJ. Clinical pharmacology of camptothecins. Cancer Chemother Pharmacol 1998;42:Suppl:S31-S43.
54. Klein CE, Gupta E, Reid JM, et al. Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. Clin Pharmacol Ther 2002;72:638-47.
55. Mathijssen RH, van Alphen RJ, Verweij J, et al. Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). Clin Cancer Res 2001;7:2182-94.
56. Iyer L, Das S, Janisch L, et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2:43-7.
57. Ando Y, Saka H, Asai G, Sugiura S, Shimokata K, Kamataki T. UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. Ann Oncol 1998;9:845-7.
58. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004; 22:1382-8.
59. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998;352:1407-12. [Erratum, Lancet 1998;352:1634.]
60. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 2000; 343:905-14.
61. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 2001;19:3801-7.
62. Goldberg RM, Sargent DJ, Morton RF, et al. N9741: FOLFOX (oxaliplatin (Oxal)/5-fluorouracil (5-FU)/ leucovorin (LV) or reduced dose R-IFL (CPT-11 + 5-FU/LV) in advanced colorectal cancer (CRC): final efficacy data from an intergroup study. J Clin Oncol 2004;22:Suppl:3621. abstract.
63. Hwang JJ, Eisenberg SG, Marshall JL. Improving the toxicity of irinotecan/5-FU/leucovorin: a 21-day schedule. Oncology (Huntingt) 2003;17:Suppl 8:37-43.
64. Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. Semin Oncol 1998;25:4-12.
65. Rixe O, Ortuzar W, Alvarez M, et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol 1996;52:1855-65.
66. Raymond E, Buquet-Fagot C, Djelloul S, et al. Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. Anticancer Drugs 1997;8:876-85.
67. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 2003;21:2059-69.
68. Raymond E, Faivre S, Chaney S, Woynarowski J, Cvitkovic E. Cellular and molecular pharmacology of oxaliplatin. Mol Cancer Ther 2002;1:227-35.
69. Grothey A. Oxaliplatin-safety profile: neurotoxicity. Semin Oncol 2003;30:Suppl: 5-13.
70. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-47.
71. Becouarn Y, Ychou M, Ducreux M, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. J Clin Oncol 1998;16:2739-44.
72. Diaz-Rubio E, Sastre J, Zaniboni A, et al. Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: a phase II multicentric study. Ann Oncol 1998;9:105-8.
73. Levi F, Perpoint B, Garufi C, et al. Oxaliplatin activity against metastatic colorectal cancer: a phase II study of 5-day continuous venous infusion at circadian rhythm modulated rate. Eur J Cancer 1993;29A:1280-4.
74. Machover D, Diaz-Rubio E, de Gramont A, et al. Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. Ann Oncol 1996;7:95-8.
75. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of ox-

aliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000;18:136-47.
76. Grothey A, Deschler B, Kroening H, et al. Phase III study of bolus 5-fluorouracil (5-FU)/ folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/ FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). In: Program and abstracts of the American Society of Clinical Oncology 38th Annual Meeting, Orlando, Fla., May 18–21, 2002. abstract.
77. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30.
78. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229-37.
79. Grothey A, Jordan K, Kellner O, et al. Randomized phase II trial of capecitabine plus irinotecan (CapIri) vs capecitabine plus oxaliplatin (CapOx) as first-line therapy of advanced colorectal cancer (ACRC). Prog Proc Am Soc Clin Oncol 2003;22:255. abstract.
80. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004;22:1209-14.
81. Saltz LB, Niedzwiecki D, Hollis D, et al. Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (FL) in stage III colon cancer (intergroup trial CALGB C89803). J Clin Oncol 2004;22:Suppl:3500. abstract.
82. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.
83. deGaramont A, Boni C, Navarro M, et al. Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: efficacy results with a median follow-up of 4 years. In: Proceedings of the 2005 Gastrointestinal Cancers Symposium, 2005:167. abstract.
84. Baselga J. Why the epidermal growth factor receptor? The rationale for cancer therapy. Oncologist 2002;7:Suppl 4:2-8.
85. Mayer A, Takimoto M, Fritz E, Schellander G, Kofler K, Ludwig H. The prognostic significance of proliferating cell nuclear antigen, epidermal growth factor receptor, and mdr gene expression in colorectal cancer. Cancer 1993;71:2454-60.
86. Hemming AW, Davis NL, Kluftinger A, et al. Prognostic markers of colorectal cancer: an evaluation of DNA content, epidermal growth factor receptor, and Ki-67. J Surg Oncol 1992;51:147-52.
87. Baselga J, Albanell J. Epithelial growth factor receptor interacting agents. Hematol Oncol Clin North Am 2002;16:1041-63.
88. Saltz L, Rubin M, Hochster H, et al. Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR). Prog Proc Am Soc Clin Oncol 2001;20:3a. abstract.
89. Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004; 22:1201-8.
90. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004; 351:337-45.
91. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/ leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003;21:60-5.
92. Kabbinavar F, Schulz J, McCleod M, et al. Bevacizumab (Avastin), a monoclonal antibody to vascular endothelial growth factor, prolongs progression-free survival in first-line colorectal cancer in subjects who are not suitable candidates for first-line CPT-11. J Clin Oncol 2004;22:Suppl:3516. abstract.
93. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
94. Saltz L, Kies M, Abbruzzese JL, Azarnia N, Needle M. The presence and intensity of the cetuximab-induced acne-like rash predicts increased survival in studies across multiple malignancies. Prog Proc Am Soc Clin Oncol 2003;22:204a. abstract.
95. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971;285: 1182-6.
96. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-76.
97. Berlin JD. Targeting vascular endothelial growth factor in colorectal cancer. Oncology (Huntingt) 2002;16:Suppl 7:13-5.
98. Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: results from the Eastern Cooperative Group (ECOG) study E2300. In: Proceedings of the 2005 Gastrointestinal Cancers Symposium, 2005:168. abstract.
99. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987-9.
100. Iqbal S, Lenz HJ. Determinants of prognosis and response to therapy in colorectal cancer. Curr Oncol Rep 2001;3:102-8.
101. Kornmann M, Schwabe W, Sander S, et al. Thymidylate synthase and dihydropyrimidine dehydrogenase mRNA expression levels: predictors for survival in colorectal cancer patients receiving adjuvant 5-fluorouracil. Clin Cancer Res 2003;9:4116-24.
102. Kornmann M, Link KH, Galuba I, et al. Association of time to recurrence with thymidylate synthase and dihydropyrimidine dehydrogenase mRNA expression in stage II and III colorectal cancer. J Gastrointest Surg 2002;6:331-7.
103. Johnston PG, Benson AB III, Catalano P, Rao MS, O'Dwyer PJ, Allegra CJ. Thymidylate synthase protein expression in primary colorectal cancer: lack of correlation with outcome and response to fluorouracil in metastatic disease sites. J Clin Oncol 2003; 21:815-9.
104. Berglund A, Edler D, Molin D, Nordlinder H, Graf W, Glimelius B. Thymidylate synthase and p53 expression in primary tumor do not predict chemotherapy outcome in metastatic colorectal carcinoma. Anticancer Res 2002;22:3653-9.
105. Aschele C, Debernardis D, Tunesi G, Maley F, Sobrero A. Thymidylate synthase protein expression in primary colorectal cancer compared with the corresponding distant metastases and relationship with the clinical response to 5-fluorouracil. Clin Cancer Res 2000;6:4797-802.
106. Innocenti F, Iyer L, Ratain MJ. Pharmacogenetics: a tool for individualizing antineoplastic therapy. Clin Pharmacokinet 2000; 39:315-25.
107. Marsh S, McLeod HL. Cancer pharmacogenetics. Br J Cancer 2004;90:8-11.