Cancer Chemother Pharmacol (2004) 54 (Suppl 1): S57–S64
DOI 10.1007/s00280-004-0888-9

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Recent phase III trials of fluorouracil, irinotecan, and oxaliplatin as chemotherapy for metastatic colorectal cancer

Published online: 7 August 2004

Abstract Colorectal cancer is a leading cause of cancer death worldwide. Recently the results of a number of well-designed clinical trials conducted across the world have led to important advances in the management of advanced colorectal cancer. These iterative studies fostered the evolution from a standard single-agent approach using fluorouracil (5-FU) to new combination regimens including capecitabine, irinotecan, and oxaliplatin in addition to 5-FU. These developments have significantly expanded the expectations of oncologists managing the disease and the options available to individuals, leading to a likelihood of extended survival compared to previous statistics. The identification of new combination chemotherapy regimens and the integration of novel targeted therapies with cytotoxic chemotherapies are areas of active clinical investigation. In this paper selected phase III studies from around the globe that tested these new chemotherapy options and led to new standards of care and better expectations for patients with advanced colorectal cancer are reviewed.

Keywords Advanced colorectal cancer · Fluorouracil · Capecitabine · Oxaliplatin · Irinotecan

This work was presented at the 19th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "State of the Arts for Digestive Organs", 14–15 November 2003, Nagoya, Japan.

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Introduction

Worldwide, colorectal cancer is the second most common malignancy and the third leading cause of cancer death taking 500,000 lives annually [40]. In the USA, the 5-year survival rate among patients diagnosed with all stages of colorectal cancer is 62%, and stage of disease remains the strongest prognostic factor [45]. Among the 25% of patients who present with distant metastases, 5-year survival is less than 10%. While significant advances have been made in recent years, cure is seldom possible in the advanced disease setting making further improvements in therapy imperative. Until the early 1990s, fluorouracil (5-FU) was the single effective chemotherapy available, but only led to meaningful responses in a small minority of treated individuals. The recent integration of oxaliplatin and irinotecan for the management of patients with advanced disease has extended median survivals in a meaningful way. Two antibodies with antitumor activity, bevacizumab and cetuximab, are in advanced stages of development and will expand options further once they become commercially available. Agents and combinations of chemotherapy agents that have been tested in the management of colorectal cancer will be discussed in the context of the best currently available evidence.

5-FU

5-FU, a fluorinated pyrimidine, has been and remains the most widely used chemotherapy employed as either a single agent or as a component of combination therapy for the treatment of colorectal cancer (see Table 1). Following metabolic activation, 5-fluoro-2′-deoxyuridylate (FdUMP) binds to methylenetetrahydrofolate (CH_2FH_4) forming a ternary complex with thymidylate synthase (TS). The ternary complex interferes with DNA synthesis by inhibiting the conversion of deoxyuridylate (dUMP) to thymidylate (dTMP). It is likely that 5-FU

Table 1 Randomized studies comparing fluorouracil to other single agents (*TTP* time to progression, *PFS* progression-free survival, *OS* overall survival, *NA* not available, *5-FU* fluorouracil, *LV* leucovorin calcium/folinic acid, *UFT* 4:1 molar ratio of uracil and tegafur)

Regimen	Reference	Number of patients	Response rate (%)	TTP or PFS (months)	Median OS (months)
Bolus 5-FU					
5-FU	42	1234	12	4.0	11.3
5-FU/LV	2	1527	23	4.0	11.9
Infused 5-FU/LV	19	188	23	4.4	14.1
	17	210	21	5.9	14.7
Single agent					
Capecitabine	27	603	26	4.6	12.9
UFT + LV	9	816	12	3.5	11.2
Raltitrexed	14	247	18	NA	10.9
Irinotecan	49	226	18	4.2	12.0
Oxaliplatin	No phase III studies				

has additional mechanisms of action that include its direct incorporation into RNA where the fraudulent pyrimidine interferes with RNA transcription. To a lesser extent, 5-FU also can be directly incorporated as a fraudulent pyrimidine into DNA. With response rates ranging from 10% to 15%, the single-agent activity of 5-FU is modest [2]. However, both activity and overall patient survival can be enhanced by the addition of the biochemical modulator leucovorin calcium (LV, also known as folinic acid). The half-life and stability of the FdUMP-TS-CH_2FH_4 ternary complex is increased in the presence of augmented concentrations of reduced folates such as LV [15].

The North Central Cancer Treatment Group (NCCTG) performed a trial for advanced colorectal cancer in the 1980s, in which 429 patients were randomized to one of six regimens: 5-FU alone, 5-FU plus high-dose or low-dose LV, 5-FU plus high-dose or low-dose methotrexate (MTX), or 5-FU plus cisplatin [44]. The two 5-FU/LV regimens (low-dose LV given with 5-FU for five consecutive days every 4 to 5 weeks and high-dose LV given with 5-FU weekly for 6 of 8 weeks) were associated with better survival when compared to 5-FU alone (12.2 and 12.0 months vs 7.7 months), 5-FU/MTX or 5-FU/cisplatin. Accrual was extended to the two 5-FU/LV arms and the 5-FU/high-dose MTX arm with an additional 259 patients enrolled. Both 5-FU/LV regimens outperformed 5-FU/MTX, and there was no significant discernible activity advantage for high-dose LV over low-dose LV [43]. A meta-analysis updated in 2003 eventually included 2751 patients with advanced colorectal cancer enrolled in 18 trials who were randomized to 5-FU/LV or 5-FU alone. In the pooled data set the addition of LV led to a doubling in response rates (23% vs 12%; $P < 0.0001$) with a modest but statistically significant improvement in 1-year survival (48% vs 43%; $P = 0.003$) [42]. In North America, two LV-modulated 5-FU regimens are most commonly employed:

1. The Mayo/NCCTG regimen: 5-FU 425 mg/m^2 per day and LV 20 mg/m^2 per day administered for five consecutive days repeated every 4 weeks for two cycles then every 5 weeks thereafter.
2. The Roswell Park regimen: 5-FU 500 mg/m^2 and high-dose LV 500 mg/m^2 administered weekly for six consecutive weeks and repeated every 8 weeks.

Both regimens are deemed to be equally effective and, until recently, were widely prescribed as they were considered to be the standards for the first-line treatment of patients with advanced colorectal cancer [8]. Toxicity differences do exist between the regimens with more grade 3/4 alopecia, mucositis and neutropenia observed in patients on the Mayo Clinic regimen and more diarrhea observed in patients on the Roswell Park regimen.

Infusional versus bolus 5-FU

5-FU has a plasma half-life of less than 15 min and its primary activity is S phase-dependent cytotoxicity. The cell-cycle specificity and short half-life after bolus administration prompted the evaluation of a number of prolonged infusion schedules as a means to expose more cells to the agent while they were in the vulnerable segment of the cell cycle [39]. In an analysis of 1219 patients with advanced colorectal cancer pooled from six randomized trials comparing continuous infusion to bolus administration of 5-FU, significantly higher response rates (22% vs 14%; $P = 0.0002$) with modest improvements in survival (median 12.1 vs 11.3 months; $P = 0.04$) were observed in patients assigned to continuous infusion 5-FU [4]. The toxicity profile for 5-FU was also schedule-dependent as the infusion regimens led to less-severe (grade 3/4) hematologic toxicity (4% vs 31%), but more frequent hand-foot syndrome (34% vs 13%). The incidence of severe diarrhea, mucositis and nausea did not differ substantially as a function of the administration schedule.

The Mayo/NCCTG bolus schedule was compared with a 48-h high-dose infusion schedule given with LV and a loading dose of 5-FU followed by a 22-h 5-FU infusion administered on two consecutive days every 2 weeks (LV5FU2) in a study conducted by a French group of investigators who enrolled 433 patients [16]. The LV5FU2 regimen led to higher response rates (32.6% vs 14.4%; $P = 0.0004$), longer progression-free survival (PFS) (27.6 vs 22 weeks; $P = 0.0012$), and showed a trend toward improved overall survival (62 vs 56.8 weeks; $P = 0.067$). Patients enrolled in the LV5FU2 arm also had less neutropenia (1.9% vs 7.3%), diarrhea (2.9% vs 7.3%), and mucositis (1.9% vs 12.7%). The enthusiasm for continuous infusion schedules has been

strong in Europe where several different infusion programs are the most common choice of treating physicians, but administration via infusion has been less widely adopted in the USA due to concerns of catheter-associated complications, inconvenience and reimbursement issues [33, 34].

Oral fluoropyrimidines

For many years medicinal chemists strove to develop oral fluoropyrimidines to provide an alternative to either bolus or continuous infusion 5-FU. 5-FU cannot be administered orally due to its inconsistent absorption and rapid catabolic clearance by dihydropyrimidine dehydrogenase (DPD). Useful oral fluoropyrimidines have been developed via two strategies: the administration of a more reliably absorbed 5-FU prodrug (e.g., capecitabine), or by combining 5-FU with inhibitors of DPD to retard its degradation (e.g., UFT and S-1). Capecitabine is reliably absorbed in the gastrointestinal tract and once absorbed undergoes conversion via a three-enzyme pathway to 5-FU. It is first metabolized in the liver to 5′-deoxy-5-fluorocytidine by carboxylesterase, and then converted in the liver and tumor tissues by cytidine deaminase to 5′-deoxy-5-fluorouridine. The enzyme responsible for the final activation step to 5-FU is thymidine phosphorylase (TP), an enzyme that is present in higher concentrations in tumor tissue than in non-neoplastic tissue [38]. There have been two randomized comparisons of capecitabine (2500 mg/m^2 per day administered twice daily for 14 of every 21 days) with bolus 5-FU/LV in a total combined sample size exceeding 1200 patients. The findings of the two studies were consistent, showing equivalent survival efficacy with a more favorable toxicity profile for capecitabine [27, 56]. In the USA, capecitabine is approved with an indication for the first-line management of advanced colorectal cancer with a fluoropyrimidine alone.

UFT is a combination, in a 4:1 molar ratio, of uracil (a competitive inhibitor of DPD) with the 5-FU prodrug, tegafur. Excess uracil competes with 5-FU as a substrate for DPD, and thus inhibits 5-FU catabolism. In randomized studies comparing UFT with oral LV (UFT/LV) to bolus 5-FU/LV, the UFT/LV regimen has demonstrated less toxicity but a similar response rate and overall survival [9, 20]. UFT is approved for use and is widely prescribed in Europe and Japan, but is not approved in the USA because of concerns about its equivalence to 5-FU/LV.

S-1 is another oral fluorinated pyrimidine derivative consisting of a fixed combination of tegafur and two 5-FU modulators: the potent DPD inhibitor 5-chloro-2,4-dihydroxypyrimidine and potassium oxonate, which inhibits 5-FU phosphorylation as a strategy meant to decrease 5-FU gastrointestinal toxicity. One European phase II study of S-1 at 40 mg/m^2 twice daily for 28 days every 5 weeks in previously untreated patients led to a response rate of 24% among 37 evaluable patients [57]. Grade 3/4 diarrhea afflicted 35% of patients. To date, no phase III studies using S-1 have been undertaken in Europe or North America. Neither UFT nor S-1 appears likely to supplant capecitabine in the USA as the oral agent of choice in either single-agent or combination therapy programs for advanced colorectal cancer.

Raltitrexed

Raltitrexed is a folate-based specific TS inhibitor. It showed promising activity and good tolerability in phase II trials when administered using a simple bolus schedule of 3.0 mg/m^2 every 21 days [58]. This prompted three large randomized comparisons of raltitrexed with bolus 5-FU/LV [10, 11, 12]. In these studies the response rates regardless of assigned treatment arm ranged from 15% to 20%, and there were no significant activity differences identified between the two arms. While in two of the trials equivalent survivals were found between arms, in the third US trial survival with raltitrexed was significantly inferior to survival with 5-FU/LV (9.7 vs 12.7 months; $P = 0.01$) [41]. Initially raltitrexed appeared to have toxicity advantages over 5-FU/LV, with less stomatitis and leukopenia. Subsequent reports of elevations in liver enzymes and increased morbidity and mortality secondary to severe diarrhea and neutropenia, especially in patients with renal compromise, have prompted recommendations for judicious monitoring of patients treated with this agent [5, 22, 24]. In a trial of 905 patients randomly assigned to either of two infusion schedules of 5-FU (de Gramont, Lokich) or raltitrexed, similar response rates and survival were reported for raltitrexed and the de Gramont regimen. However treatment with raltitrexed resulted in greater gastrointestinal and hematological toxicity and patients reported an inferior quality of life [37]. While no longer under active evaluation in the USA, raltitrexed is in use regionally in Europe and South America.

Irinotecan

Irinotecan (also known as CPT-11) is a semisynthetic derivative of the plant alkaloid camptothecin which inhibits the function of the enzyme topoisomerase I. Topoisomerase I permits relaxation of supercoiled DNA by inducing reversible and transient single-stranded DNA breaks that are sufficient to permit replication. Irinotecan is a prodrug that requires conversion by a carboxylesterase-converting enzyme to SN-38, its active metabolite. SN-38 stabilizes the DNA-topoisomerase complex, thus preventing separation of the replicating forks, and this replication fork arrest results in apoptosis [53]. The dose-limiting toxicity of irinotecan is delayed-onset diarrhea. It appears that intestinal β-glucuronidase, which hydrolyzes a detoxified SN-38 metabolite to active SN-38, causes intestinal epithelial damage and

leads to diarrhea. A unique toxicity observed in some patients is an acute syndrome, characterized by diaphoresis, salivation, lacrimation, abdominal cramps and bradycardia, This acute syndrome responds to atropine and is felt to be a cholinergic effect consequent upon the structure of the drug [52].

Two European studies evaluated single-agent irinotecan as a second-line treatment. In one trial Rougier and colleagues compared irinotecan to continuous 5-FU and found improved overall survival (10.8 vs 8.5 months; $P = 0.035$) and median time to progression (4.2 vs 3.9 months; $P = 0.030$) favoring the irinotecan arm [48]. The second study by Cunningham and colleagues compared irinotecan plus best supportive care to best supportive care without chemotherapy. The patients treated on the irinotecan arm manifested improved overall survival of 9.2 vs 6.5 months ($P = 0.0001$) [13].

Subsequently, two studies performed in previously untreated patients receiving first-line chemotherapy established the activity and toxicity profile of the combination of irinotecan with 5-FU/LV and identified the regimen as an important option for patients with advanced colorectal cancer (see Table 2). Among 683 patients randomized to irinotecan plus bolus 5-FU/LV (IFL), 5-FU/LV, or irinotecan alone, IFL led to an improved response rate (39% vs 21%; $P = 0.001$) and overall survival (14.8 vs 12.6 months; $P = 0.04$) when compared to 5-FU/LV [49]. Results for irinotecan monotherapy were similar to 5-FU/LV.

These findings were consistent with an earlier study reported by Douillard and colleagues indicating a superior response rate (35% vs 22%; $P < 0.001$) and survival (17.4 vs 14.1 months; $P = 0.031$) for patients receiving irinotecan coupled with weekly or biweekly infusions of 5-FU/LV compared to the infusion of 5-FU/LV alone [19]. In subsequent trials, concerns regarding IFL toxicity have been raised. To investigate these concerns the National Cancer Institute, USA, convened an independent panel of colorectal cancer experts to review and report their findings on an unexpected number of early deaths in two cooperative group studies involving IFL within 60 days of patient enrollment on study [46]. The majority of deaths were associated with multiple gastrointestinal toxicities or various thromboembolic events, prompting recommendations for vigilant clinical monitoring and aggressive supportive intervention for patients experiencing toxicity after treatment with IFL.

Oxaliplatin

Oxaliplatin is a third-generation, platinum-based compound with a 1,2-diaminocyclohexane (DACH) carrier ligand, which forms DNA adducts and results in strand breaks. Unlike other platinum-based agents, oxaliplatin had activity in preclinical model systems of colorectal cancer. It is thought that the activity distinctive among currently available platinum-based agents may be due to the bulky DACH ligand that interferes more effectively, based upon its steric properties, with mechanisms of DNA repair inducing apoptosis [36, 54]. Oxaliplatin has two types of distinctive sensory neurotoxicity. Acute cold-induced sensory neuropathy that is characterized by dysesthesias and paresthesias occurs during or soon after the infusion. A delayed-onset, dose-dependent neuropathy can occur hours to days after repeated treatments. The latter typically occurs in 10–15% of patients after a cumulative dose of 780–850 mg/m^2. The chronic neuropathy exhibits either complete or partial reversibility in 75% of affected patients within 3 to 5 months of treatment discontinuation. Both the acute and chronic sensory neuropathy may be attenuated by prolonging the infusion time from 2 to 6 h and by adding calcium and magnesium infusions before and after oxaliplatin infusions [23].

Table 2 Results of studies comparing combination chemotherapy regimens to single agents or to other doublets (*PFS* progression free survival, *TTP* time to progression, *OS* overall survival, *IFL* weekly bolus 5-FU/LV + irinotecan, *FOLFIRI* biweekly infusional plus bolus 5-FU/LV + irinotecan, *FUFIRI* weekly infusional 5-FU/LV + irinotecan, *FOLFOX* biweekly infusional plus bolus 5-FU/LV + oxaliplatin, *FUFOX* weekly infusional 5-FU/LV + oxaliplatin, *IROX* irinotecan + oxaliplatin)

Reference	Regimen	Number of patients	Response rate (%)	TTP or PFS (months)	Median OS (months)
Single agent vs combination therapy					
49	Irinotecan	226	18	4.2	12.0
	5-FU/LV Mayo	226	21	4.3	12.6
	IFL	231	39	7.0	14.8
19	Infused 5-FU/LV	188	23	4.4	14.1
	FOLFIRI	198	41	6.7	17.4
17	LV5FU2	210	21	5.9	14.7
	FOLFOX	210	49	8.9	16.2
Combination vs combination therapy					
55	FOLFOX	111	56	8.1	20.6
	FOLFIRI	109	54	8.5	21.5
26	IROX	264	34	6.5	17.4
	IFL	264	31	6.9	14.8
	FOLFOX	267	45	8.7	19.5

Oxaliplatin administered alone exhibits single-agent activity in 18–20% of chemotherapy-naive patients and in 10% of patients who have previously failed 5-FU therapy [6, 7, 18, 35]. When administered with 5-FU/LV, oxaliplatin produces response rates of 20–26% in 5-FU-refractory disease [1]. Results from a randomized, multicenter trial comparing infusional 5-FU/LV (LV5FU2), single-agent oxaliplatin, and the combination (FOLFOX) in 821 patients with recurrence following IFL demonstrate superior outcomes for patients assigned to FOLFOX with higher response rates (9.6% vs 1.1% oxaliplatin vs 0% LV5FU2; $P < 0.0001$) and longer time to progression (4.2 vs 1.6 vs 2.1 months; $P = 0.07$) [47]. Despite this, no significant survival advantage for the FOLFOX regimen was noted.

Promising first-line trial results were reported in two important studies conducted in Europe. The first compared FOLFOX with LV5FU2. Improved PFS (9.0 vs 6.2 months; $P = 0.0003$) was seen, but there was no significant improvement in overall survival. However, the trial was powered for a PFS endpoint and was insufficiently powered for survival as an endpoint (16.2 vs 14.7 months; $P = 0.12$) [17]. Chronomodulated infusions of 5-FU alone or with oxaliplatin were compared in the second trial which noted improved responses rates (53% vs 19%; $P < 0.001$) and PFS (8.7 vs 6.1 months; $P = 0.048$) with the addition of oxaliplatin [25]. A survival advantage for FOLFOX has been confirmed in a three-arm NCCTG-led intergroup trial (N9741) of patients with advanced colorectal cancer randomly assigned to bolus IFL, FOLFOX or a combination of irinotecan plus oxaliplatin (IROX) [26]. FOLFOX was associated with better response rates (45% vs 31%; $P = 0.002$), longer time to progression (8.7 vs 6.9 months; $P = 0.0014$), and improved median survival (19.5 vs 14.8 months; $P = 0.0001$) compared to IFL. FOLFOX was also superior to IROX. At present, either oxaliplatin or irinotecan in combination with 5-FU/LV (preferably as an infusion regimen) represent reasonable strategies for first-line chemotherapy in patients with unresectable metastatic colorectal cancer.

Comparison of irinotecan or oxaliplatin plus 5-FU infusion regimens

A single completed study comparing an oxaliplatin- to an irinotecan-based regimen coupled with bolus and then infused 5-FU and LV (FOLFOX 4 vs FOLFIRI) has been reported [55]. In this study, patients crossed over to the alternative treatment arm upon progression while on their first regimen. The primary endpoint of this study was PFS on second-line therapy. Because the trial was powered for PFS as the endpoint, only 226 patients were enrolled. The PFS on second-line therapy was a problematic endpoint because one-third of patients received only a single line of therapy. However the results are intriguing despite this difficulty. The overall response rate (ORR) was 56% for FOLFIRI in first line and 4% for FOLFIRI in second line. For FOLFOX the ORR was 54% in first line and 15% in second line. The P values for these comparisons all exceeded 0.50. While these patients were initially judged to be unresectable, sufficient responses were observed in 22% of the FOLFOX- and 9% of the FOLFIRI-treated patients to permit surgical interventions that culminated in complete resections in the majority of patients. The overall PFS on first-line therapy was 8.5 months for FOLFIRI and 8.1 months for FOLFOX ($P = 0.24$). The second-line PFS was 2.5 months for FOLFIRI and 4.2 months for FOLFOX ($P = 0.003$). The overall median survival did not differ between strategies at 21.5 months with FOLFIRI/FOLFOX and 20.6 months with FOLFOX/FOLFIRI ($P = 0.99$). Higher rates of grade 3/4 febrile neutropenia, alopecia, nausea and stomatitis occurred with FOLFIRI, while neutropenia and paresthesias were more common with FOLFOX. This study indicates equivalent activity and moderate toxicity differences between these two strategies, suggesting that either is reasonable.

Intrahepatic chemotherapy

In colorectal cancer, the liver is the most frequent site of distant metastases. The liver has a unique dual blood supply: the hepatic vein serves as the primary source of oxygen and nutrition for the healthy parenchyma while the hepatic artery provides the majority of the blood supply to metastatic intrahepatic tumors. This differential blood supply underlies the rationale for intrahepatic chemotherapy delivered via hepatic artery infusion (HAI). Fluorodeoxyuridine (FUDR) is the preferred agent for HAI because of its short half-life and high rate of hepatic extraction leading to a 100- to 400-fold ratio of hepatic to systemic drug exposure [21].

The true clinical utility of HAI remains uncertain. A meta-analysis including 654 patients with unresectable hepatic metastases enrolled in seven randomized trials comparing HAI to systemic 5-FU therapy for advanced liver disease did show greater tumor response rates with HAI (41% vs 14%; $P < 0.001$), but no survival advantage (16 vs 12.2 months; $P = 0.14$) [3]. Kerr and colleagues randomized 209 patients to systemic therapy (LV5FU2) or HAI with 5-FU/LV [32]. No differences in PFS or overall survival (14.7 vs 14.8 months; $P = 0.79$) were observed. However, because of technical challenges inherent to HAI, 37% of HAI-assigned patients did not start their treatment and an additional 29% were unable to receive more than two cycles due to catheter failure. A later study enrolled 117 patients with liver-limited unresectable metastases who were randomized to bolus 5-FU/LV or HAI with FUDR [31]. Response rates (51% vs 24%; $P = 0.009$) and survival (22.7 vs 19.8 months; $P = 0.027$) favored HAI, although time to extrahepatic progression was significantly shorter for HAI patients (7.8 vs 23 months; $P = 0.0007$). The clinical implications of this study are uncertain, in part due to its

very slow accrual (reflecting a highly selected population), the use of a 5-FU/LV control regimen which is no longer a first-line standard for advanced disease, and the fact that the majority of patients were enrolled at a single institution. With the availability of more efficacious systemic multiagent chemotherapy regimens, the value of HAI in unresectable advanced CRC is currently limited. A role for HAI therapy with an adjuvant intent has been suggested for patients with resected liver metastases, but is outside the scope of this review [30].

Development of novel agents

An improved understanding of the molecular pathogenesis of cancer has advanced the development of novel agents designed to target critical cellular pathways. Two of these agents, cetuximab (C225) and bevacizumab, have reached the stage of development that includes either randomized phase II or phase III testing. Cetuximab is a chimeric monoclonal antibody against the epidermal growth factor receptor (EGFR). In a phase II trial of cetuximab given as monotherapy in 57 patients with $EGFR^+$ colorectal cancer refractory to both 5-FU and irinotecan, 11% of patients achieved a partial response [51]. A large phase II trial of 121 patients treated with cetuximab plus irinotecan was reported at ASCO in 2001 [50]. The response rate in patients who had prior exposure to irinotecan was 19% and the duration of response was 186 days. Subsequently the results of the trial from Europe were presented at the 2003 ASCO meeting [14]. This extended phase II study employed a 2:1 randomization scheme such that 218 patients who were known to express EGFR and had progression after treatment with irinotecan were assigned to cetuximab plus irinotecan and 111 patients were assigned to cetuximab alone. Response rates were 23% to cetuximab plus irinotecan and 11% to cetuximab alone. These results indicate that antibody therapies are active even in a treatment-refractory population.

Perhaps the most exciting recent development in treatment of metastatic colorectal cancer targets tumor neovascularization, suggesting that the long wait for an active antiangiogenic therapy may be over. Bevacizumab (rhu-Mab-VEGF; Avastin) is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF). In a phase II trial of low-dose or high-dose bevacizumab for advanced disease, the addition of low-dose bevacizumab to 5-FU/LV resulted in longer median survival (21.5 vs 13.8 months) [29]. The results of a first-line phase III trial in 815 patients with metastatic colorectal cancer randomized to IFL versus IFL plus bevacizumab were reported at ASCO 2003 [28]. The combination was associated with improved response rates (45% vs 35%; $P = 0.0029$), PFS (10.6 vs 6.2 months; $P < 0.00001$) and median survival (20.3 vs 15.6 months; $P = 0.00003$). An unusual, but easily treated toxicity, grade 3 hypertension, was noted to be higher with bevacizumab (10.9% vs 2.3%), but no increases in bleeding or thrombotic events were observed. Bevacizumab remains investigational at this time and is being studied in combination with FOLFOX. Ongoing studies will better define the promise of these new approaches and the optimal strategies for their deployment. However, it appears that the options for therapy will continue to expand based on these early results.

Conclusions

Current evidence supports the use of 5-FU/LV in combination with irinotecan or oxaliplatin for patients with unresectable advanced colorectal cancer. Capecitabine represents an oral treatment option for patients who are not candidates for multiagent chemotherapy due to preference, logistics or comorbid disease. Regional chemotherapy intraarterial infusion (HAI) may be an option for patients with liver-limited unresectable metastases, particularly in the setting of clinical investigations. While current chemotherapy practices are primarily defined by cytotoxic therapies, the integration of targeted therapies is imminent and holds the promise of further improving outcomes for patients with colorectal cancer.

References

1. Andre T, Louvet C, Raymond E, Tournigand C, de Gramont A (1998) Bimonthly high-dose leucovorin, 5-fluorouracil infusion and oxaliplatin (FOLFOX3) for metastatic colorectal cancer resistant to the same leucovorin and 5-fluorouracil regimen. Ann Oncol 9:1251
2. [Anonymous] (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project. J Clin Oncol 10:896
3. [Anonymous] (1996) Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. Meta-Analysis Group in Cancer. J Natl Cancer Inst 88:252
4. [Anonymous] (1998) Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. Meta-Analysis Group in Cancer. J Clin Oncol 16:301
5. [Anonymous] (1999) Drug-company decision to end cancer trial. Lancet 354:1045
6. Becouarn Y, Rougier P (1998) Clinical efficacy of oxaliplatin monotherapy: phase II trials in advanced colorectal cancer. Semin Oncol 25 [2 Suppl 5]:23
7. Becouarn Y, Ychou M, Ducreux M, Borel C, Bertheault-Cvitkovic F, Seitz JF, Nasca S, Nguyen TD, Paillot B, Raoul JL, Duffour J, Fandi A, Dupont-Andre G, Rougier P (1998) Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. J Clin Oncol 16:2739
8. Buroker TR, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Mailliard JA, Schaefer PL, Levitt R, Kardinal CG, Gesme DH Jr (1994) Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 12:14
9. Carmichael J, Popiela T, Radstone D, Falk S, Borner M, Oza A, Skovsgaard T, Munier S, Martin C (2002) 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 20:3617
10. Cocconi G, Cunningham D, Van Cutsem E, Francois E, Gustavsson B, van Hazel G, Kerr D, Possinger K, Hietschold SM (1998) Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. J Clin Oncol 16:2943
11. Cunningham D (1998) Mature results from three large controlled studies with raltitrexed ('Tomudex'). Br J Cancer 77 [Suppl 2]:15
12. Cunningham D, Zalcberg JR, Rath U, Oliver I, van Cutsem E, Svensson C, Seitz JF, Harper P, Kerr D, Perez-Manga G (1996) Final results of a randomised trial comparing 'Tomudex' (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. "Tomudex" Colorectal Cancer Study Group. Ann Oncol 7:961
13. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413
14. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Van Cutsem E (2003) Cetuximab (C225) alone or in combination with irinotecan (CPT-11) in patients with epidermal growth factor receptor (EGFR)-positive, irinotecan-refractory metastatic colorectal cancer (MCRC) (abstract 1012). Proc Am Soc Clin Oncol 22:252
15. Danenberg PV, Danenberg KD (1978) Effect of 5,10-methylenetetrahydrofolate on the dissociation of 5-fluoro-2′-deoxyuridylate from thymidylate synthetase: evidence for an ordered mechanism. Biochemistry 17:4018
16. de Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL, Morvan F, Louvet C, Guillot T, Francois E, Bedenne L (1997) 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 15:808
17. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938
18. Diaz-Rubio E, Sastre J, Zaniboni A, Labianca R, Cortes-Funes H, de Braud F, Boni C, Benavides M, Dallavalle G, Homerin M (1998) Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: a phase II multicentric study. Ann Oncol 9:105
19. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041
20. Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, Vincent MD, Lembersky BC, Thompson S, Maniero A, Benner SE (2002) 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 20:3605
21. Ensminger WD (2002) Intrahepatic arterial infusion of chemotherapy: pharmacologic principles. Semin Oncol 29:119
22. Ford HE, Cunningham D (1999) Safety of raltitrexed. Lancet 354:1824
23. Gamelin E, Gamelin L, Bossi L, Quasthoff S (2002) Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol 29 [5 Suppl 15]:21
24. Garcia-Vargas JE, Sahmoud T, Smith MP, Green S (1999) Qualitative and chronological assessment of toxicities during treatment with raltitrexed (Tomudex) in 861 patients: implications for patient management (abstract 222). Eur J Cancer 35 [Suppl 4]:S72
25. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Levi F (2000) Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136
26. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23
27. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO, Wong R (2001) 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 19:2282
28. Hurwitz HI, Fehrenbacher T, Cartwright J, Hainsworth J, Heim W, Berlin J, Griffing S, Novotny W, Holmgren E, Kabbinavar F (2003) Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC (abstract 3646). Proc Am Soc Clin Oncol 22:3464a
29. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E (2003) Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21:60
30. Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, Bertino JR, Turnbull AD, Sullivan D, Stockman J, Blumgart LH, Fong Y (1999) Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 341:2039
31. Kemeny NE, Niedzwiecki D, Hollis R, Lenz H-J, Naughton MJ, Weeks JC, Herndon JE, Zhang K, Mayer RJ (2003) Hepatic arterial infusion (HAI) versus systemic therapy for hepatic metastases from colorectal cancer; a CALGB randomized trial of efficacy, quality of life (QOL), cost effectiveness, and molecular mark (abstract 1010). Proc Am Soc Clin Oncol 22:252
32. Kerr DJ, McArdle CS, Ledermann J, Taylor I, Sherlock DJ, Schlag PM, Buckels J, Mayer D, Cain D, Stephens RJ; Medical Research Council Colorectal Cancer Study Group; European Organisation for Research and Treatment of Cancer Colorectal Cancer Study Group (2003) Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. Lancet 361:368
33. Macdonald JS (1989) Continuous low-dose infusion of fluorouracil: is the benefit worth the cost? J Clin Oncol 7:412
34. Macdonald JS, Astrow AB (2001) Adjuvant therapy of colon cancer. Semin Oncol 28:30
35. Machover D, Diaz-Rubio E, de Gramont A, Schilf A, Gastiaburu JJ, Brienza S, Itzhaki M, Metzger G, N'Daw D, Vignoud J, Abad A, Francois E, Gamelin E, Marty M, Sastre J, Seitz JF, Ychou M (1996) 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 7:95
36. Mathe G, Kidani Y, Triana K, Brienza S, Ribaud P, Goldschmidt E, Ecstein E, Despax R, Musset M, Misset JL (1986) A

phase I trial of trans-l-diaminocyclohexane oxalato-platinum (l-OHP). Biomed Pharmacother 40:372
37. Maughan TS, James RD, Kerr DJ, Ledermann JA, McArdle C, Seymour MT, Cohen D, Hopwood P, Johnston C, Stephens RJ; British MRC Colorectal Cancer Working Party (2002) Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. Lancet 359:1555
38. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274
39. Myers CE, Diasio R, Eliot HM, Chabner BA (1976) Pharmacokinetics of the fluoropyrimidines: implications for their clinical use. Cancer Treat Rev 3:175
40. Parkin DM (2001) Global cancer statistics in the year 2000. Lancet Oncol 2:533
41. Pazdur R, Vincent M (1997) Raltitrexed (Tomudex) versus 5-fluorouracil and leucovorin (5-FU and LV) in patients with advanced colorectal cancer (ACC): results of a randomized, multicenter, North American trial (abstract 801). Proc Am Soc Clin Oncol 16
42. Piedbois P, Michiels S for the Meta-Analysis Group in Cancer (2003) Survival benefit of 5FU/LV over 5FU bolus in patients with advanced colorectal cancer: an updated meta-analysis based on 2,751 patients (abstract 1180). Proc Am Soc Clin Oncol 22:294
43. Poon MA, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Tschetter LK, Levitt R, Kardinal CG, Mailliard JA (1991) Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J Clin Oncol 9:1967
44. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA, Laurie JA, Tschetter LK (1989) Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7:1407
45. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Fay MP, Feuer EJ, Edwards BK (eds) (2003) SEER Cancer Statistics Review, 1975–2000. National Cancer Institute. Bethesda. http://seer.cancer.gov/csr/1975_2000
46. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19:3801
47. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, Burger BG, Le Bail N, Haller DG (2003) 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 21:2059
48. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407
49. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343:905
50. Saltz L, Rubin M, Hochster H, Tchekmeydian NS, Waksal H, Needle M, LoBuglio A (2001) Cetuximab (IMC-C225) plus Irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR) (abstract 7). Proc Am Soc Clin Oncol 20:7a
51. Saltz L, Meropol NJ, Loehrer PJ, Waksal H, Needle MN, Mayer RJ (2002) Single agent IMC-C225 (Erbitux) has activity in CPT-11-refractory colorectal cancer (CRC) that expresses the epidermal growth factor receptor (EGFR) (abstract 504). Proc Am Soc Clin Oncol 21:504a
52. Takasuna K, Hagiwara T, Hirohashi M, Kato M, Nomura M, Nagai E, Yokoi T, Kamataki T (1996) Involvement of beta-glucuronidase in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride (CPT-11) in rats. Cancer Res 56:3752
53. Takimoto CH, Arbuck SG (2001) Topoisomerase I targeting agents: the camptothecins. In: Chabner BA, Longo DL (eds) Cancer chemotherapy and biotherapy: principles and practice. Lippincott, Williams & Wilkins, Philadelphia, p 579
54. Tashiro T, Kawada Y, Sakurai Y, Kidani Y (1989) Antitumor activity of a new platinum complex, oxalato (trans-l-1,2-diaminocyclohexane)platinum (II): new experimental data. Biomed Pharmacother 43:251
55. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229
56. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P; Xeloda Colorectal Cancer Study Group (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 19:4097
57. Van den Brande J, Schoffski P, Schellens JH, Roth AD, Duffaud F, Weigang-Kohler K, Reinke F, Wanders J, de Boer RF, Vermorken JB, Fumoleau P (2003) EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. Br J Cancer 88:648
58. Zalcberg JR, Cunningham D, Van Cutsem E, Francois E, Schornagel J, Adenis A, Green M, Iveson A, Azab M, Seymour I (1996) ZD1694: a novel thymidylate synthase inhibitor with substantial activity in the treatment of patients with advanced colorectal cancer. Tomudex Colorectal Study Group. J Clin Oncol 14:716