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First-Line Treatment Strategies to Improve Survival in Patients with Advanced Colorectal Cancer

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Abstract

Advanced colorectal cancer is a significant cause of worldwide cancer-related mortality. For the majority of patients, palliative chemotherapy can yield substantial improvements in survival. Fluorouracil has been the mainstay of treatment in this setting for the past few decades. The relatively recent availability of new combinations with active agents such as irinotecan and oxaliplatin makes this a promising and hopeful time for the treatment of metastatic colorectal cancer, with median survivals now approaching 18–21 months. For patients presenting with resectable metastases, the goal of therapy is surgery with a curative intent. There exists the potential for this approach to be extended also to a greater proportion of patients whose cancer may be rendered resectable following effective neoadjuvant chemotherapy. In addition, an improved understanding of molecular predictors for treatment response and toxicity may facilitate the future selection of individualised treatments for a given tumour profile. Further improvements in the management of advanced disease will continue to be pursued through the ongoing development of multimodality approaches and the incorporation of novel targeted agents with innovative chemotherapy combinations.

Colorectal cancer is the third leading cause of cancer death worldwide with over 800 000 related deaths every year.[1] Of the estimated 150 000 patients newly diagnosed in the US in 2002,[2] 25–30% presented with distant metastases. In addition, patients presenting with localised colorectal cancer carry a considerable future risk of recurrence and cancer-related death despite a complete resection and adjuvant therapy. The burden of advanced colorectal cancer, therefore, remains significant with a 5-year survival of <5%.[3,4]

Despite these sobering statistics, there has been progress in our management of advanced disease. Until the early 1990s, systemic treatment options were primarily limited to fluorouracil (5-fluorouracil; 5-FU) with median survival estimates of 8–12 months compared with 3–6 months with best supportive care alone.[5,6] The last decade has seen the addition of several new chemotherapy agents to the armamentarium for colorectal cancer management with consequent improvements in median survival now projected to approach almost 2 years. We have also recognised that surgical resection can

yield a curative outcome for a small but meaningful proportion of selected patients with liver-limited oligometastases. This review focuses on an evidence-based discussion of the development of first-line treatment strategies to improve survival for patients with advanced colorectal cancer.

1. Systemic Chemotherapy for Advanced Disease

The goals of chemotherapy in advanced disease are to prolong survival and improve quality of life. For patients with metastatic colorectal cancer, palliative chemotherapy is associated with significant improvements in survival. In a year 2000 systematic review of 13 randomised trials comparing chemotherapy with supportive care, chemotherapy was associated with improvements in time to progression (10 vs 6 months) and overall survival (11.7 vs 8 months).[7] The quality of evidence relating to symptom control and improvement of quality of life was deemed to be insufficient. 5-FU was the most widely employed agent in these trials and the integration of newer agents, particularly irinotecan and oxaliplatin, has been associated with further advances in both response rates and the magnitude of survival benefit associated with palliative chemotherapy.

1.1 Fluorouracil (5-FU)

5-FU represents an early example of a rationally designed drug. Developed in 1957,[8] this fluorinated pyrimidine is a prodrug which primarily exerts its antineoplastic activity by inhibition of thymidylate synthase (TS), an enzyme involved in DNA synthesis. Following metabolic activation to 5-fluoro-2′-deoxyuridylate (FdUMP), it combines with methylenetetrahydrofolate (CH_2FH_4) to form a ternary complex with TS, thus inhibiting the normal conversion of deoxyuridylate (dUMP) to thymidylate (dTMP), and resulting in inhibition of DNA synthesis through depletion of required thymidine nucleotides. Additional mechanisms of action include direct incorporation into RNA to interfere with RNA transcription and, to a lesser extent, direct incorporation into DNA. With response rates of <10–15%, the activity of 5-FU as a single agent is modest,[9] prompting interest in strategies to enhance the cytotoxic activity of 5-FU without significantly increasing its toxicity. Key among these strategies has been biomodulation and variations in schedules of administration.

1.1.1 Biochemical Modulation of 5-FU

Biomodulation refers to the selective enhancement of the anti-tumour activity of 5-FU by manipulation of its biochemical mechanism of action.[10] Leucovorin calcium, also known as folinic acid, citrovorum factor or 5-formyl-tetrahydrofolate, is the most widely applied agent for the biomodulation of 5-FU. In the TS catalysed normal conversion reaction of uridylate to thymidylate, CH_2FH_4 must donate a methyl group to dUMP. FdUMP replaces dUMP in this reaction forming a covalently linked FdUMP-TS-CH_2FH_4 ternary complex leading to the inhibition of TS. Preclinical studies demonstrated an increased stability and half-life of this ternary complex in the presence of increased concentrations of reduced folates such as folinic acid (leucovorin; LV).[11] Subsequent trials[10,12] attempted to address whether this pharmacokinetic advantage would translate into a meaningful clinical advantage for 5-FU plus folinic acid versus 5-FU alone.

In a North Central Cancer Treatment Group (NCCTG)-led trial, which proved to be pivotal in the establishment of 5-FU/folinic acid as a standard regimen for advanced colorectal cancer, 429 patients were randomised to one of six regimens: 5-FU alone, 5-FU plus high-dose folinic acid (Machover regimen), 5-FU plus low-dose folinic acid (Mayo/NCCTG regimen), 5-FU plus high-dose methotrexate, 5-FU plus low-dose methotrexate or 5-FU plus cisplatin.[10] The two 5-FU/folinic acid regimens (given for 5 consecutive days every 4–5 weeks) were associated with superior survival when compared with 5-FU alone (12.2 and 12.0 months vs 7.7 months), 5-FU/methotrexate or 5-FU/cisplatin. In an expanded accrual of 259 additional patients to the 5-FU/folinic acid arms and the 5-FU/high-dose methotrexate arm, 5-FU/folinic acid remained the superior regimen with no significant advantage of high-dose over low-dose folinic acid.[12]

A subsequent meta-analysis reported a comparison of tumour response rates and overall survival using individual patient data from nine randomised trials of 5-FU/folinic acid versus 5-FU alone.[9] While this analysis of 1381 evaluable patients established the potentiated cytotoxicity of folinic acid-modulated regimens with improvements in response rates (23% vs 11%, $p < 10^{-7}$), this improvement did not translate into a survival difference (11.5 vs 11 months, $p = 0.57$). In a recent update of this analysis based on 2751 patients, a doubling in responses rate with folinic acid was confirmed in addition to a small but statistically significant improvement in survival (1-year survival 48% vs 43%, hazard ratio 0.88, $p = 0.003$).[13] These meta-analyses did not attempt to address toxicity.

Following the widespread acceptance of folinic acid-modulated schedules in advanced colorectal cancer,[14] two popular regimens emerged in North America.

- The Mayo/NCCTG Regimen: 5-FU 425 mg/m^2/day and folinic acid 20 mg/m^2/day administered for 5 consecutive days repeated every 4 weeks for two cycles then every 5 weeks thereafter.
- The Roswell Park regimen: 5-FU 500 mg/m^2 and high-dose folinic acid 500 mg/m^2 administered weekly for 6 consecutive weeks and repeated every 8 weeks.

In a randomised comparison of weekly low-dose folinic acid (20 mg/m^2) with high-dose folinic acid, no significant differences were observed in response rates or survival, although there was a greater incidence of diarrhoea in the high-dose arm.[15] The NCCTG sought to compare the Mayo/NCCTG and Roswell Park regimens in a randomised trial of 362 patients with advanced disease.[16] No significant differences were seen for tumour response (35% vs 31%, respectively) or median survival (9.3 vs 10.7 months). In terms of toxicity, more leukopenia (29% vs 5%) and stomatitis (24% vs 2%) was observed with the Mayo/NCCTG schedule, while the Roswell Park schedule was associated with a greater incidence of diarrhoea (32% vs 18%) and hospitalisation (31% vs 21%). In the absence of data supporting the superior efficacy of either of these regimens, both are deemed to be equivalent and, until recently, were considered to be the standard first-line treatment for North American patients with advanced colorectal cancer.

It is important to note that other agents have been investigated as potential biomodulators of 5-FU, particularly the antifolates including methotrexate and trimetrexate. As an inhibitor of dihydrofolate reductase (DHFR), methotrexate interferes with purine synthesis. When administered before 5-FU, methotrexate enhances the direct incorporation of 5-FU into RNA and DNA by increasing available pools of phosphoribosyl pyrophosphate via inhibition of purine synthesis, which favours the anabolic conversion of 5-FU to required 5-FU nucleotides. In addition, DHFR inhibition increases levels of polyglutamated reduced folate which enhances the binding of FdUMP to TS. In an 1178 patient meta-analysis, 5-FU/methotrexate was associated with improved response rates when compared with 5-FU alone (19% vs 10%).[17] However, this combination was inferior to 5-FU/folinic acid in the multi-arm NCCTG trial.[10,12] Attempts at 'double-modulation' with 5-FU/folinic acid/methotrexate failed to demonstrate improved efficacy over 5-FU/folinic acid in a randomised comparison by the Nordic Gastrointestinal Tumor Adjuvant Therapy Group.[18] Trimetrexate is a nonclassical folate antagonist which, unlike methotrexate, does not compete with folinic acid for intracellular transport or metabolic activation by polyglutamation.[19] Despite encouraging phase 2 data,[20] the addition of trimetrexate to a regimen of 5-FU/folinic acid did not significantly improve response rates, progression-free survival or overall survival in two recent randomised phase 3 trials.[21,22]

1.1.2 Infusional versus Bolus 5-FU

Notwithstanding the extensive worldwide clinical experience with 5-FU, controversy regarding the optimal schedule of administration still exists. 5-FU has a short plasma half-life and its cytotoxicity is S-phase dependent, prompting researchers to investigate the application of prolonged 5-FU infusions.[23] In 1998, the Meta-analysis Group in Cancer[24] published a pooled analysis of six randomised

Table I. Common infusional schedules of fluorouracil (5-FU)

Regimen (country)	Agents	Dose	Duration (h)	Interval
LV5FU2[a]/de Gramont et al.[26] (France)	LV	200 mg/m^2	2	Day 1 and 2 every 2 weeks
	5-FU	400 mg/m^2	Bolus	
	5-FU	600 mg/m^2	22	
Simplified LV5FU2[a] (France)[28]	LV	400 mg/m^2	2	Day 1 every 2 weeks
	5-FU	400 mg/m^2	Bolus	
	5-FU	2400–3000 mg/m^2	46	
AIO[29] (Germany)	LV	500 mg/m^2	2	Weekly × 6 every 8 weeks
	5-FU	2600 mg/m^2	24	
TTD[30] (Spain)	5-FU	3500 mg/m^2	48	Weekly
MAOP/Lokich et al.[31] (USA)	5-FU	300 mg/m^2/day	24	Days 1–28 continuous infusion

a LV5FU2 is a 48-hour biomodulated infusion schedule of 5-FU and high-dose LV administered every 2 weeks.

AIO = Arbeitsgemeinschaft fur Internistische Onkologie; **h** = hours; **LV** = folinic acid (leucovorin); **MAOP** = Mid-Atlantic Oncology Program; **TTD** = Spanish Group for Gastrointestinal Tumor Therapy.

trials that compared continuous infusion 5-FU regimens with bolus administration of 5-FU in patients with advanced colorectal cancer. Using individual data from 1219 patients, this analysis reported 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) in patients assigned to continuous infusion 5-FU. The toxicity profile for 5-FU was also altered in the infusional regimen with significantly less haematological toxicity (4% vs 31%) but more frequent hand-foot syndrome (34% vs 13%). The incidence of diarrhoea, mucositis and nausea did not differ between the two treatment groups. Differences in response rate and toxicity for different schedules of the same drug may be attributed to the administration of a higher dose intensity of 5-FU with a continuous infusion regimen and differences in mechanism of action. It is suggested that the RNA effects of 5-FU may be more prominent with bolus administration, while infusional 5-FU mediates its cytotoxicity via TS inhibition.[25]

The authors of this meta-analysis further attempted to address whether the addition of biomodulation to an infusional 5-FU regimen would confer enhanced efficacy. In a subgroup analysis, the benefit of continuous infusion over bolus 5-FU was not apparent in trials that used biomodulation of 5-FU with folinic acid, although the power for such an analysis was recognisably limited. However, in a subsequent French intergroup study,[26] the Mayo/NCCTG bolus schedule was compared with a 48-hour high-dose biomodulated infusion schedule administered every 2 weeks (LV5FU2). In this trial involving 433 patients, LV5FU2 was associated with higher response rates (32.6% vs 14.4%, p = 0.0004), longer progression-free survival (27.6 vs 22 weeks, p = 0.0012) and a trend towards improved overall survival (62 vs 56.8 weeks, p = 0.067). The LV5FU2 arm was also associated with less neutropenia (1.9% vs 7.3%), diarrhoea (2.9% vs 7.3%) and mucositis (1.9% vs 12.7%). This schedule is described in table I, along with other commonly employed infusional regimens. While widely used in Europe, the enthusiasm for continuous infusion regimens of 5-FU has been somewhat dampened in the US secondary to concerns of increased cost, risk of catheter-associated complications and patient inconvenience.[27]

1.2 Oral Fluoropyrimidines

Oral fluoropyrimidines may represent a less cumbersome alternative to continuous infusional 5-FU with the associated advantage of sustained cytotoxic exposure and improved tolerability. Because of its poor bioavailability and rapid catabolic clearance by dihydropyrimidine dehydrogenase (DPD), 5-FU has been unsuitable for oral delivery. Strategies in the development of alternate oral fluoropyrimidines have included the use of a 5-FU prodrug (capecitab-

ine) and combination regimens with inhibitors of DPD.

Capecitabine is well absorbed as an intact molecule by the gastrointestinal tract and undergoes a three-step enzymatic conversion to 5-FU. First metabolised in the liver by carboxylesterase to 5′-deoxy-5-fluorocytidine, it is converted in the liver and tumour tissues by cytidine deaminase to 5′-deoxy-5-fluorouridine. Finally, a tumour-selective phenomenon is facilitated by higher intratumoural activity of thymidine phosphorylase (TP), the enzyme responsible for the final step of its conversion to 5-FU.[32] A randomised comparison led by the University of Texas MD Anderson Cancer Center[33] of capecitabine (2500 mg/m^2/day administered twice daily for 14 of every 21 days) with bolus 5-FU/folinic acid in 605 patients with advanced colorectal cancer showed higher overall response rates in the capecitabine group (24.8% vs 15.5%, p = 0.005) with similar disease-free and overall survival.[33] Patients treated with capecitabine had a lower incidence of diarrhoea, stomatitis and myelosuppression with a greater incidence of hand-foot syndrome and hyperbilirubinaemia. In a trial with a similar design in 602 patients, European investigators published findings confirming the equivalent efficacy and more favourable toxicity profile of capecitabine with bolus 5-FU/folinic acid.[34] In the US, capecitabine is currently approved for the first-line management of advanced colorectal cancer when a fluoropyrimidine alone is indicated. Because of concerns of tolerability at full dose (2500 mg/m^2/day), particularly among the elderly, starting doses of capecitabine are often adjusted to 75% (2000 mg/m^2/day).

Tegafur/uracil (UFT) is an oral agent which combines uracil, a competitive inhibitor of DPD, with the 5-FU prodrug tegafur in a 4 : 1 molar ratio. Excess uracil competes with 5-FU for DPD, thus inhibiting 5-FU catabolism. In two randomised comparisons with bolus 5-FU/folinic acid, UFT with oral folinic acid demonstrated less toxicity but similar efficacy in terms of response rate and overall survival.[35,36] While approved for use in Europe and Japan, UFT has not garnered approval by the FDA for use in the US.

Eniluracil (5-ethynyluracil) is a potent irreversible oral inhibitor of DPD, which results in its complete inactivation. When administered with low oral doses of conventional 5-FU, eniluracil permits the attainment of 5-FU steady-state concentrations similar to those obtained by continuous infusion of 5-FU.[37] However, eniluracil combined with oral 5-FU resulted in an inferior overall survival when compared with bolus 5-FU/folinic acid[38] and efforts targeting a new drug application for its use were discontinued by the manufacturer.

Finally, S-1 is another new oral fluorinated pyrimidine derivative. Developed in Japan, S-1 is a fixed combination of tegafur and two 5-FU modulators: 5-chloro-2,4-dihydroxypyrimidine (a DPD inhibitor 200 times more potent than uracil) and potassium oxonate (an inhibitor of 5-FU phosphorylation expected to decrease the gastrointestinal toxicity of 5-FU). In a phase 1 trial, diarrhoea was the dose-limiting toxicity despite the potassium oxonate.[39] A European phase 2 study of S-1 at 40 mg/m^2 twice daily for 28 days every 5 weeks in 37 previously untreated patients with advanced colorectal cancer reported a partial response in nine evaluable patients (24%), stable disease in 17 (46%) and progressive disease in 11 (30%).[40] Grade 3 to 4 diarrhoea was experienced by 35% of patients. Given its toxicity and the absence of data supporting superior efficacy over capecitabine, the role of this investigational agent in the current management of advanced colorectal cancer is uncertain.

1.3 Raltitrexed

As previously discussed in section 1.1, TS is a critical enzyme in DNA synthesis. Unlike fluoropyrimidines, raltitrexed is a folate-based direct and specific TS inhibitor. Promising activity and tolerability in phase 2 trials using a convenient 3-weekly bolus schedule (3.0 mg/m^2 every 21 days)[41] prompted three large, randomised comparisons of raltitrexed with bolus 5-FU/folinic acid.[42-44] Response rates of 15–20% were reported across all three studies, with no significant differences identi-

fied between the two arms. However, in the US trial, overall survival was inferior with raltitrexed (9.7 vs 12.7 months), with no survival differences reported in the remaining two studies. With less stomatitis and leukopenia, raltitrexed was believed to have a more favourable toxicity profile, although reports of elevations in liver enzymes and increased morbidity and mortality secondary to severe diarrhoea and neutropenia has prompted recommendations for more judicious monitoring with this agent.[45,46] Patients with diminished renal function are at a particularly high risk for toxicity.

In a recent three-arm trial of 905 patients randomly assigned to one of two infusional schedules of 5-FU (de Gramont or Lokich regimens; see table I) or raltitrexed, similar response rates and survival were reported for raltitrexed and the de Gramont regimen, but raltitrexed resulted in greater gastrointestinal and haematological toxicity and an inferior quality of life.[47] Of interest, a subsequent multinational European trial in the adjuvant setting (Pan European Trial in Adjuvant Colon Cancer [PETACC]-1[48]) was prematurely suspended by the drug company following findings of increased drug related deaths with raltitrexed compared with 5-FU/folinic acid controls (1.9% vs 0.8%).[48] While currently not under active evaluation in the US, raltitrexed remains an agent of investigation for advanced colorectal cancer in Canada and is commercially available in several countries in Europe and South America.

1.4 Pemetrexed

Pemetrexed is a new generation multitargeted antifolate which interrupts purine and pyrimidine synthesis via inhibition of three key enzymes involved in folate metabolism: TS, DHFR and glycinamide ribonucleotide formyltransferase. Two phase 2 studies of pemetrexed 600 mg/m^2 every 21 days have been reported in previously untreated patients with advanced colorectal cancer. In the first trial, grade 4 neutropenia and thrombocytopenia in three of nine patients mandated a dose reduction to 500 mg/m^2.[49] Of 29 evaluable patients, a 17% overall response rate was observed with a grade 3 rash in 13 patients (ameliorated by dexamethasone) and grade 3–4 neutropenia in 7 of 23 patients treated at the lower dose. The second study reported a 15% overall response rate among 39 evaluable patients with grade 3–4 neutropenia in 55%, thrombocytopenia in 18% and grade 3 rash in 53% of patients.[50] Phase 1/2 studies of pemetrexed in combination with irinotecan or oxaliplatin are currently being conducted.

1.5 Irinotecan

A semisynthetic derivative of the plant alkaloid camptothecin, irinotecan (also known as CPT-11) is an inhibitor of DNA topoisomerase I (topo I). During DNA replication, topo I facilitates the unwinding of DNA by generating reversible and transient single-stranded DNA breaks. As topo I is the cellular target of irinotecan, it is postulated that increased expression of intratumoural topo I may predict for anti-tumour response to irinotecan. This has been supported by preclinical evidence[51-53] and a small retrospective study of 11 patients with 5-FU refractory advanced colorectal cancer.[54] In this series, high *topo I* gene expression (measured by reverse transcriptase polymerase chain reaction [RT-PCR]) correlated with responsiveness to irinotecan; however, a consistent predictive association between pretreatment topo I expression and response is yet to be demonstrated. Following the enzymatic conversion of irinotecan to its active metabolite, SN-38, cytotoxicity is mediated by the stabilisation of these otherwise transient DNA breaks with replication arrest and resultant cell death when these cleavage complexes collide with moving DNA replication forks. SN-38 is conjugated to its inactive metabolite by uracil diphosphate-glucuronosyltransferase (UGT1A1). Therefore, irinotecan is contraindicated in patients with impaired UGT1A1 activity (Crigler-Najjar syndrome, Gilbert's syndrome). Principal toxicities include a delayed onset diarrhoea, neutropenia, nausea and vomiting, alopecia and an acute cholinergic-like syndrome characterised by diaphoresis, salivation, lacrimation, abdominal cramps and bradycardia occurring during or immediately following infusion. This responds

promptly to atropine. Irinotecan-induced diarrhoea has a typical onset of 24 hours after infusion, peaking at days 5 or 6. It is hypothesised that this dose-limiting toxicity is induced by SN-38 glucuronide, a detoxified SN-38 metabolite which is hydrolysed by intestinal β-glucuronidase to active SN-38, thus causing damage to intestinal epithelium and consequent diarrhoea.[55]

Building on phase 2 results supporting the antitumour activity of irinotecan in 5-FU-resistant disease,[56] two randomised European trials (V302/V301) of second-line therapy were reported in 1998.[57,58] Both trials used an every 3 weeks regimen with a starting dose of 350 mg/m^2 and demonstrated improvements in survival for patients after 5-FU failure when compared with continuous infusion 5-FU (10.8 vs 8.5 months)[57] or best supportive care (9.2 vs 6.5 months).[58] Following the 1998 US FDA approval of irinotecan as monotherapy for second-line treatment of patients refractory to 5-FU, phase 2 trials in the US reported objective response rates of 26–32% in chemotherapy-naïve patients using a weekly regimen of 125 mg/m^2.[59,60] Both trials also identified significant leukopenia (22%) and diarrhoea (29–36%).

In light of its promising activity and distinct mechanism of action, regimens were developed combining irinotecan with 5-FU/folinic acid. Reflecting preferences in clinical practices, a weekly (4 of every 6) bolus schedule (IFL) was pursued in the US (5-FU 125 mg/m^2 + 500 mg/m^2 and folinic acid 20 mg/m^2), while European schedules combined bolus irinotecan with weekly (80 mg/m^2 + Arbeitsgemeinschaft fur Internistische Onkologie [AIO]) or biweekly (180 mg/m^2 + LV5FU2) infusional regimens. An amendment of the latter schedule, replacing LV5FU2 with simplified LV5FU2, has been coined the FOLFIRI regimen.[61]

In the year 2000, two important trials contributed to the North American approval of irinotecan in combination with 5-FU/folinic acid as first-line therapy for advanced colorectal cancer. In trial 0038 led by Saltz and colleagues[62] and conducted in the US, Canada, Australia and New Zealand, 683 patients were randomly assigned to IFL, 5-FU/folinic acid or irinotecan monotherapy. When compared with 5-FU/folinic acid, the IFL regimen was associated with superior response rates and overall survival. As summarised in table II, these findings were consistent with the earlier results from Douillard and colleagues[63] in the 385 patient multinational V303 trial from Europe, Israel and South Africa comparing irinotecan combined with weekly or biweekly infusional 5-FU/folinic acid with infusional 5-FU/folinic acid alone. In a subsequent combined analysis of these trials, the authors[64] concluded that irinotecan plus 5-FU/folinic acid would henceforth represent the reference standard for comparison of future first-line therapies for metastatic colorectal cancer.

It is important to note that concerns regarding toxicity with the weekly bolus IFL combination were raised in July 2001. N9741 is an NCCTG-led phase 3 intergroup trial that initially compared five

Table II. Phase III trials of irinotecan combined with fluorouracil (5-FU) and folinic acid (leucovorin; LV)

Outcome	Study 0038[62]		V303[63]	
	5-FU/LV bolus (n = 221)	Irinotecan + bolus 5-FU/LV (n = 222)	5-FU/LV infusional (n = 188)	Irinotecan + infusional 5-FU/LV (n = 199)
Response rate (%)	21	39 (p < 0.001)	22	35 (p < 0.005)
Median time to progression (mo)	4.3	7.0 (p = 0.004)	4.4	6.7 (p < 0.001)
Median survival (mo)	12.6	14.8 (p = 0.04)	14.1	17.4 (p = 0.031)
Grade 3 or greater[a] toxicity (% patients)				
diarrhoea	13	23	6	14
vomiting	4	10	2	4
febrile neutropenia	15	7	1	3
neutropenia	67	54	14	46

a National Cancer Institute – Common Toxicity Criteria.

mo = months.

Table III. Treatment arms in N9741[65]

Arm	October 1998	March 2000 amendment
Mayo/NCCTG	5-FU 425 mg/m^2 + LV 20 mg/m^2 d1–5 every 3wk (control arm)	Terminated because of inferior efficacy – IFL new control arm
IFL	Irinotecan 125 mg/m^2+ 5-FU 500 mg/m^2 + LV 20 mg/m^2 weekly × 4/6	Continued
Sequential	Irinotecan 275 mg/m^2 d1 + (5-FU 400 mg/m^2 + LV 20 mg/m^2) d2–5 every 3wk	Terminated because of toxicity (5 deaths among 61 patients)
Wasserman	Oxaliplatin 85 mg/m^2 + irinotecan 200 mg/m^2 d1 every 3wk	Continued
Bolus	Oxaliplatin 130 mg/m^2 + 5-FU 320 mg/m^2 + LV 20 mg/m^2 d1–5 every 3wk	Terminated because of toxicity (3 deaths among 16 patients)
DeGramont (FOLFOX4)	Oxaliplatin 85 mg/m^2 d1 + (5-FU 400 mg/m^2 bolus + LV 200mg/m^2 then 5-FU 600mg/m^2 infusion × 22h) d1 and 2, every 2wk	Continued

5-FU = 5-fluorouracil; **d** = days; **h** = hours; **LV** = folinic acid (leucovorin); **wk** = weeks.

investigational combination regimens with a control arm of Mayo/NCCTG 5-FU/folinic acid (table III). Through the implementation of a real-time toxicity monitoring system, the study was amended in March 2000 from a six-arm trial to a three-arm trial with the termination of two experimental arms because of unexpectedly high death rates[65] and, consequent to the reporting of the two trials mentioned above, the displacement of 5-FU/folinic acid with IFL as the new control arm. In April 2001, accrual to N9741 was suspended because of a disproportionate number of deaths in the first 60 days of study entry among patients on the IFL control arm (4.8% IFL vs 1.8% FOLFOX vs 1.8% Wasserman [see table III for regimens]).[66] An independent expert panel was convened to review the data from N9741 and C89803, a Cancer and Leukemia Group B intergroup trial of patients randomised to IFL or 5-FU/leucovorin (Roswell Park regimen) in the adjuvant setting. The majority of IFL deaths in both studies were attributed to gastrointestinal toxicities and the unexpected finding of an excess number of thromboembolic events.[67] A heightened awareness regarding IFL-related gastrointestinal and vascular toxicity, close clinical monitoring and early recognition of toxicity with aggressive supportive treatment intervention is recommended for patients receiving IFL.

1.6 Oxaliplatin

Platinum derivatives such as cisplatin and carboplatin have had no definable antitumour activity in colorectal cancers. Oxaliplatin (also known as L-OHP) is a diaminocyclohexane (DACH) platinate belonging to the third generation of platinum derivatives with demonstrated activity in cisplatin-resistant tumours, including tumours of the colorectum.[68,69] While the mechanisms of action of cisplatin and oxaliplatin are similar, including DNA binding, adduct formation and strand breaks, the reasons for the differential cytotoxicity of oxaliplatin are poorly understood. At least in part, the activity of oxaliplatin in colorectal cancers has been attributed to the DACH carrier ligand which, when retained by the oxaliplatin-formed DNA adducts, may alter the mechanisms of DNA repair which have typically been associated with cisplatin resistance.[70]

Oxaliplatin has a unique pattern of adverse effects. Unlike other platinums, it causes no significant nephrotoxicity, ototoxicity or alopecia.[71,72] Beyond mild-to-moderate haematological and gastrointestinal toxicity, phase 1 clinical trials of oxaliplatin monotherapy reported a dose-limiting neurotoxicity manifested as an acute sensory neuropathy and a late-onset cumulative sensory neuropathy.[73,74] The acute neuropathy is characterised by transient cold-induced distal dysaesthesias and paraesthesias occurring during or soon after infusion. These are generally mild but common,

occurring in >80% of patients.[72] Rarely, a transient pharyngolaryngeal dysaesthesia may occur, creating a feeling of dyspnea or dysphagia. These symptoms may be accompanied by cold-dependent and involuntary muscular cramps of the extremities or jaw. Prolonging the duration of infusion from 2 hours to 6 hours may ameliorate these acute symptoms. However, the delayed sensory neuropathy is characterised by persistent dysaesthesias and paraesthesias of the extremities with a dose-related progression which may be experienced by 10–15% of patients after a cumulative dose of 780–850 mg/m^2. Similarly to the neuropathy seen with cisplatin, these symptoms may progress to include impaired sensation, sensory ataxia or impairment of fine sensory-motor coordination. Motor neurons and motor function are typically spared.[72] At least partial reversibility of neurotoxicity is seen in 75% of affected patients within 3–5 months of therapy discontinuation.

Earlier phase 2 clinical trials of oxaliplatin reported single agent activity in 18–20% of chemotherapy-naïve patients[75,76] and in 10% of patients with 5-FU refractory disease.[75,77] Subsequent phase 2 trials of oxaliplatin combined with 5-FU/folinic acid showed higher response rates of 20–26% in patients who previously did not respond to 5-FU therapy,[78] suggesting that the combination of oxaliplatin and 5-FU is indeed synergistic.

In March 2000, two randomised European trials of first-line oxaliplatin plus 5-FU/folinic acid versus 5-FU/folinic acid alone in advanced colorectal cancer[79,80] were presented to the US FDA for an application of oxaliplatin as first-line therapy. At this time oxaliplatin was already approved for use in several European countries. In one trial, 420 patients were randomly assigned to oxaliplatin 85 mg/m^2 plus LV5FU2 (FOLFOX4) or LV5FU2 alone every 2 weeks.[79] The primary endpoint was progression-free survival, which was significantly longer for the oxaliplatin combination regimen (9.0 vs 6.2 months, $p = 0.0003$). The study was not powered to detect an improvement in overall survival which, although increased in the FOLFOX4 arm (16.2 vs 14.7 months), did not reach statistical significance ($p = 0.12$).

In the second trial, 200 patients were randomised to receive a 5-day chronomodulated infusion course of 5-FU/folinic acid with or without oxaliplatin on day 1.[80] Chronomodulated infusions of 5-FU are administered at variable rates over 24 hours to coincide with circadian differences in TS activity and DPD levels. While chronomodulation has been associated with lower toxicity and improved response rates,[81,82] the true merit of this approach is not established and, thus, has not gained widespread acceptance as a standard schedule. This is due, in part, to the need for programmable pumps in order to permit chronomodulated 5-FU infusions. The addition of oxaliplatin was associated with improved response rates (53% vs 19%, $p < 0.001$) and progression-free survival (8.7 vs 6.1 months, $p = 0.048$) in this study, but no significant improvements were seen for overall survival (19.9 vs 19.4 months). Despite higher response rates, the lack of a statistically significant survival advantage and the somewhat unorthodox methodology of the second trial led the Oncology Drug Advisory Committee to reject the application for oxaliplatin as first-line treatment. Subsequently, in August 2002, oxaliplatin in combination with LV5FU2 (FOLFOX4) was approved by the US FDA as a second-line schedule for patients with recurrence or progression within 6 months of completing IFL. This approval was based on the interim analysis of a multicentre, randomised, second-line trial (EFC4584) of 5-FU/folinic acid (as LV5FU2), single-agent oxaliplatin and FOLFOX4 in 459 patients with recurrence following IFL.[83] Patients randomised to FOLFOX4 had higher response rates (9.9% vs 1.3% oxaliplatin vs 0% LV5FU2) and longer time to progression (4.6 vs 1.6 vs 2.7 months). This trial heightened awareness of the lack of significant activity with oxaliplatin alone in a second-line setting, emphasising the importance of administering both oxaliplatin and 5-FU/folinic acid in patients refractory to IFL.

The benefit of oxaliplatin in the first-line setting has since been confirmed by N9741, a three-arm intergroup trial of patients randomised to IFL, FOLFOX4 or a combination of irinotecan plus oxaliplatin (table III).[84] Presented at the American

Table IV. Results from N9741[84] (see table III for details of treatment regimens)

Outcome	IFL[a] (control; n = 264)	FOLFOX4 (n = 267)[b]	Oxaliplatin + Irinotecan (n = 264)
Response rate (%)	31	45 (p = 0.002)	34 (p = 0.03)
Median time to progression (mo)	6.9	8.7 (p = 0.0014)	6.7 (p = NS)
Median survival (mo)	14.8	19.5 (p = 0.002)	17.4 (p = 0.04)
Grade 3 or greater toxicity (% patients)			
paraesthesias	3	18[c]	7
diarrhoea	28	12[c]	24
vomiting	14	3[c]	22
febrile neutropenia	15	4[c]	11

a 24% of patients received oxaliplatin-based treatment on progression.

b 60% of patients received irinotecan-based treatment on progression.

c IFL vs FOLFOX4, p < 0.002.

mo = months; **NS** = nonsignificant.

Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, Illinois, 31 May–3 June 2003,[85] N9741 demonstrated superior response rates, time to progression and overall survival with FOLFOX4 when compared with IFL (table IV). With the exception of paraesthesias, toxicity data also favoured FOLFOX4 with less nausea, vomiting, diarrhoea and febrile neutropenia. Despite some uncertainty regarding potential imbalances in the availability of second-line treatments and the contribution of the infusional 5-FU approach to the overall magnitude of FOLFOX4 benefit, it is evident from this data that FOLFOX represents a regimen of major importance in the first-line treatment of advanced colorectal cancer. As the data were immature for the oxaliplatin/irinotecan arm, the true efficacy of this regimen is currently undefined.

Of interest, in the colorectal session at ASCO 2002, Grothey et al.[86] presented the results of a phase 3 German trial of bolus 5-FU/folinic acid (Mayo/NCCTG) versus oxaliplatin plus 5-FU/folinic acid in a modified AIO regimen (FUFOX). With 236 randomised evaluable patients, FUFOX was associated with higher response rates (49% vs 23%, p < 0.001) and improved progression-free survival (7.8 vs 5.3 months, p = 0.001) with a statistically nonsignificant improvement in overall survival (21.4 vs 16.1 months, p = 0.19). The impressive 21.4 month median survival reported in the FUFOX arm was attributed to the contribution of effective salvage therapies. In a provocative analysis of previous randomised trials, Grothey et al.[86] demonstrated a linear association between a prolonged median survival and the successive availability of 5-FU, irinotecan and oxaliplatin, thus emphasising the need for access to all three active agents in order to significantly impact on the survival of patients with advanced colorectal cancer.

1.7 Which Regimen as First-Line?

After decades of offering 5-FU/folinic acid as the lone systemic therapy for patients with unresectable metastatic disease, oncologists are now faced with a new but welcome dilemma of having to select an appropriate first-line regimen from a menu of available options, including 5-FU/folinic acid, capecitabine, irinotecan with or without 5-FU/folinic acid, or oxaliplatin with or without 5-FU/folinic acid. For patients with a poor performance status or significant comorbidity, single agent therapy is an appropriate consideration. However, for the majority of patients eligible for combination chemotherapy, the optimal choice of a first-line regimen with oxaliplatin or irinotecan remains controversial. In a noteworthy report at ASCO, San Francisco, California, 12-15 May 2001, Tournigand et al.[87] (Oncology Multidisciplinary Research Group [GERCOR]) presented the results of a multicentre phase 3 trial of FOLFIRI followed by FOLFOX6 (oxaliplatin 100mg/m^2 and simplified LV5FU2 every 2 weeks) versus FOLFOX6 followed by FOLFIRI in previously untreated patients with metastatic colorectal

cancer. With the objective of determining the best therapeutic sequence, 226 patients were randomised with crossover at progression. As shown in table V, both sequences were equivalent with, once again, impressive median survivals exceeding 20 months. It is unknown at this time whether the higher proportion of patients with complete surgical resection achieved with the FOLFOX-FOLFIRI sequence will ultimately translate into improved 5-year survival rates.

While the efficacy results of N9741 (comparing FOLFOX4 with bolus IFL) and the comparative toxicity profile demonstrated by the GERCOR study would tend to support FOLFOX as a preferred regimen, its superiority over irinotecan plus 5-FU/folinic acid in the first-line setting cannot be definitively declared at this time. Hence, for the present, the selection of either oxaliplatin plus 5-FU/folinic acid or irinotecan plus 5-FU/folinic acid is appropriate for the first-line management of reasonable performance status patients with unresectable metastatic colorectal cancer. In the future, clinical decisions regarding optimal therapy for the individual patient may be guided by a tumour assessment for molecular predictors of chemosensitivity and treatment-related toxicity.

1.8 Predicting Treatment Response and Toxicity

In an attempt to select patient-tailored treatments, studies of molecular markers in colorectal cancer have explored several potential determinants of both prognostic and predictive value. Most notable among these are microsatellite instability (MSI) and TS. Colorectal cancer is the consequence of a series of genetic alterations resulting in the transformation of an abnormal cell to a malignant cell, as initially described by the 'adenoma-carcinoma' sequence.[88] Presently coined the chromosomal instability pathway, this sequence of successive mutations and loss of heterozygosity of a series of tumour suppressor loci is implicated in 85% of colorectal cancers.[89] The remaining 15% are associated with a second more subtle form of genetic instability due to a disruption of the DNA mismatch repair system. Known as the MSI pathway (or MIN), the phenotypic hallmark of MIN is variation in the length of microsatellites, that is, small DNA sequences re-

Table V. Results from the Oncology Multidisciplinary Research Group (GERCOR) Study: FOLFIRI[a] followed by FOLFOX6[b] versus FOLFOX6 followed by FOLFIRI (Tournigand et al.[87])

Outcome	FOLFIRI-FOLFOX6		FOLFOX6-FOLFIRI	
Response rate (%)				
first-line	57		56	
second-line	21		7	
Resection after first-line (%)	7		18	
Median time to progression after two lines of therapy (mo)	14.4		11.5	
Median survival (mo)	20.4		21.5	
Grade 3 or greater toxicity by regimen (% patients)	**FOLFIRI**	**FOLFOX6**	**FOLFOX6**	**FOLFIRI**
neurotoxicity[c]	0	20	34	20
diarrhoea	14	5	11	9
alopecia	24	9	9	13
febrile neutropenia	6	0	1	1
neutropenia	25	17	44	31

a FOLFIRI = irinotecan 180 mg/m^2 + 5-FU bolus 400 mg/m^2 + LV 200 mg/m^2 followed by 5-FU 2.4–3 g/m^2 46-hour infusion every 2 weeks.

b FOLFOX6 = oxaliplatin 100 mg/m^2 + 5-FU bolus 400 mg/m^2 + LV 200 mg/m2 followed by 5-FU 2.4–3 g/m^2 46-hour infusion every 2 weeks.

c Specific Modified Levy scale.

5-FU = fluorouracil; **LV** = folinic acid (leucovorin); **mo** = months.

peated in tandem throughout the genome.[85] In the localised setting, tumours with high levels of MSI (MSI-H) appear to have a better prognosis with a decreased likelihood of metastases.[90,91] Questions regarding the predictive value of MSI were raised by retrospectively generated data from a nonrandomised cohort which had suggested that MSI may be a marker for efficacy of 5-FU-based adjuvant therapy.[92] These findings were contradicted by a recent molecular analysis of 570 pooled tissue specimens from randomised 5-FU-based adjuvant chemotherapy trials.[93] Patients with MSI-H tumours had a better outcome confirming the work of previous investigators. However, there was a trend towards worse outcomes with therapy ($p = 0.07$) suggesting pending confirmation that adjuvant 5-FU may not be warranted for patients with MSI-H tumours. Although the prognostic or predictive role of MSI-H in advanced disease has not yet been defined, this remains a question of significant interest.

TS, the target enzyme of 5-FU, represents the most extensively evaluated determinant of predictive value in the metastatic setting. Low levels of TS have been associated with improved survival.[94,95] In a cohort of 46 advanced patients receiving 5-FU/folinic acid, low intratumoural TS mRNA expression was associated with both higher response rates and improved survival.[96] Similar findings were reported when TS levels were evaluated by immunohistochemistry. Among 108 patients with advanced colorectal cancer, TS-negative tumours had higher 5-FU response rates when compared with TS-positive tumours (30% vs 15%, $p < 0.04$).[97] TP and DPD are also germane. Colorectal tumours with low expression of all three genes by RT-PCR were shown to have an improved response to 5-FU therapy, whereas nonresponders were found to have high expression of at least one of these genes.[98] While these series do support the value of a low TS level as a favourable predictor of 5-FU response, efforts have shifted from an evaluation of TS protein or RNA expression to an evaluation of variants in the responsible gene. A polymorphism in the enhancer region of the TS promoter can influence levels of TS expression, with the triple repeat homozygote (L/L) correlating with higher intratumoural TS levels than are seen in those with the double repeat homozygotes (S/S) or with heterozygotes (S/L).[99,100] In an examination of 50 patients with advanced colorectal cancer treated with 5-FU, individuals with the S/S homozygous genotype demonstrated a superior 50% response rate compared with 9% in those with L/L,[100] suggesting that genotyping for the TS polymorphism may identify patients more likely to respond to 5-FU-based chemotherapy.

In addition to predicting response to therapy, the emerging field of pharmacogenetics is a tool for identifying genetic predictors of toxicity. Mutations in the gene encoding DPD, the initial and rate-limiting enzyme of 5-FU catabolism, have been identified in patients with severe toxicity after 5-FU therapy.[101-103] The potential implications of this finding are significant given that the population prevalence of DPD deficiency is estimated to be 3–5%.[104] For the prodrug irinotecan, inactivation and biliary excretion of its active metabolite, SN-38, requires glucuronide conjugation via the hepatic enzyme UGT1A1.[105] A polymorphism in the TATA sequence of the UGT1A1 gene promoter has been associated with lower SN-38 glucuronidation rates and greater irinotecan toxicity.[106]

Collectively, these data demonstrate that genetic predictors of response and toxicity have the potential to segregate patients into clinically meaningful profiles for a guided selection of therapy. Prospective investigations in this exciting field, along with the ongoing development of multiplex high-throughput technologies, will be required to establish the future utility of predictive markers in our clinical decision making for patients with advanced colorectal cancer

2. Regional Management of Liver Limited Metastases

Up to 25% of patients with colorectal cancer will present with synchronous liver metastases at the time of diagnosis.[107] In addition, the liver is the dominant site of recurrence in almost 50% of patients whose cancer recurs following a curative primary resection. The potential curative benefit of

surgical resection in patients with metastases limited to the liver is clear, with a 5-year survival attainable in over one-third of patients with resected cancer.[108] Typically contraindicated in patients with extensive bilobar involvement, exciting new operative strategies such as sequential hepatic resections, *ex vivo* tumour resections and preoperative portal vein embolisation procedures (to induce hypertrophy of the remnant lobe) have further pushed the definition of resectability. The dogma of exclusion in the presence of extra-hepatic disease has also been challenged for selected patients with solitary pulmonary metastases amenable to resection.[109] In addition, nonsurgical methods of hepatic tumour ablation, including cryotherapy, ethanol injection or radiofrequency ablation, offer an alternative regional therapy for lesions not amenable to surgical resection or in patients who are at an unacceptably high risk of surgical complications.

Unfortunately, recurrences are observed in two-thirds of patients after resection of liver metastases. The role of post-resection 'adjuvant' therapy with systemic 5-FU/folinic acid remains debatable and is not established as a standard approach. A randomised intergroup trial of 5-FU plus levamisole with or without folinic acid was terminated early because of poor accrual. However, a preliminary analysis of enrolled patients demonstrated a 5-year survival of 50% in both arms.[110]

The dual blood supply of the liver with preferential perfusion of metastases by the hepatic artery has made the prospect of hepatic arterial infusion therapy (HAI) appealing.[111] In a meta-analysis of seven randomised trials for unresectable hepatic metastases, HAI with floxuridine (fluorodeoxyuridine; FUDR) was associated with improved response rates (41% vs 14%, $p < 0.001$) without a significant survival advantage (15 vs 12.2 months, $p = 0.14$) when compared with systemic 5-FU-based therapy.[111] However, in the adjuvant setting, systemic 5-FU/folinic acid alternating with HAI with FUDR may improve survival, as reported in a randomised study following resection of liver-limited metastases, with 2-year overall survival rates of 86% with 5-FU/folinic acid plus HAI and 72% with 5-FU/folinic acid alone.[112] In a second randomised intergroup trial comparing hepatic resection alone with hepatic resection followed by HAI and continuous systemic infusion of 5-FU, 4-year recurrence-free rates were improved for the chemotherapy group (46% vs 25%, $p = 0.04$) with no significant improvement in median survival (63.7 vs 49 months, $p = 0.60$).[113] The questionable efficacy of adjuvant HAI and its associated demands and toxicity have limited the acceptance of this approach. Whether more effective systemic chemotherapy can obviate the need for hepatic infusion therapy remains the subject for future trials.

The recent availability of more efficacious combination regimens has raised the possibility of altering the natural history for patients with unresectable disease by downstaging tumours with primary chemotherapy and rendering them amenable to a potentially curative resection. In a series of 151 patients with unresectable liver-limited colorectal metastases, resection following systemic therapy with oxaliplatin plus 5-FU/folinic acid was attempted in 51%, with a complete resection achieved in 38%.[114] The 5-year survival rate for the resected cohort of 77 patients was 50%. While this experience represents a selected group of patients, it does imply that a neoadjuvant approach may expand the scope of patients with advanced colorectal cancer who may be amenable to a curative-intent approach.

3. Future Directions

The search for novel agents for the management of advanced colorectal cancer has led to the exploration of myriad potential targets including the epidermal growth factor receptor (EGFR), angiogenic factors, matrix metalloproteinases and cyclo-oxygenases.

Of the several agents under investigation, cetuximab (C225-ImClone Systems Inc., New York, NY, USA), a chimeric monoclonal antibody against EGFR, has progressed the furthest in its development as a targeted therapy for colorectal cancer. In a phase 2 trial of cetuximab monotherapy in 57 patients with EGFR+ colorectal cancer refractory to both 5-FU and irinotecan, objective responses were

seen, with 6 patients (11%) achieving a partial response.[115] First-line trials of cetuximab with irinotecan/5-FU/folinic acid are currently underway.

In another application of monoclonal antibody therapy, Kabbinavar and colleagues[116] reported a randomised phase 2 trial of low-dose or high-dose bevacizumab (recombinant humanised monoclonal antibody to vascular endothelial cell growth factor) plus 5-FU/folinic acid and 5-FU/folinic acid alone. In the treatment of metastatic colorectal cancer, the addition of bevacizumab to 5-FU/folinic acid resulted in improved objective response rates and overall survival (18.0 vs 13.6 months). Exciting early results from a phase 3 trial of 815 patients randomised to first-line bevacizumab 5 mg/kg with IFL or IFL alone were reported at ASCO 2003.[117] The combination was associated with improved response rates (45% vs 35%, $p = 0.0029$), progression-free survival (10.6 vs 6.2 months, $p < 0.00001$) and overall survival (20.3 vs 15.6 months, $p = 0.00003$). Bleeding and thrombotic events were not increased with bevacizumab, although hypertension was more common (10.9% vs 2.3%). A second Eastern Cooperative Oncology Group trial (E3200) is evaluating bevacizumab plus FOLFOX in patients who progressed on IFL.

Clinical trials of new targets in combination with conventional chemotherapy will define their impact and future role in the management of patients with colorectal cancer.

Beyond the ongoing pursuit of new agents, much still remains to be defined regarding the optimal use of currently available therapies. What is the best possible integration of these agents and in what sequence? Would early exposure to a triple therapy oxaliplatin plus irinotecan plus 5-FU combination further improve patient outcomes? Will oral capecitabine replace infusional 5-FU/folinic acid in first-line combination regimens with oxaliplatin or irinotecan? These questions remain the subject of active investigation in phase 1/2 clinical trials and will hopefully be elucidated in the near future.

4. Conclusions

As has been reviewed in this article, there has been significant progress in the management of patients with metastatic colorectal cancer. This has been accomplished through a deliberate and thoughtful process of scientific data gathering by means of well designed clinical trials and multinational collaborative efforts. It is known that palliative chemotherapy is better than best supportive care. The long established first-line standard of 5-FU/folinic acid has now been supplanted by the emergence of capecitabine and combination regimens with irinotecan and oxaliplatin. The availability of these agents as first-line and sequential therapies has translated into significant improvements in median survival, now approaching 2 years in clinical trial populations. In certain patients, the therapeutic goal has advanced from palliation to curability. Patients with resectable liver limited disease are candidates for surgery with curative intent. A combined modality approach with neoadjuvant chemotherapy followed by surgery may alter the natural history for patients with unresectable metastases limited to the liver. In addition, the development and integration of novel targeted agents offers the continued hope and opportunity to further improve the quality of life and survival for patients with advanced colorectal cancer.

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