

CHAPTER 20 THE ROLE OF SYSTEMIC CHEMOTHERAPY IN METASTATIC DISEASE

20.1 To treat or not to treat

First- and second-line chemotherapy should be considered standard treatment for patients with metastatic Colorectal Cancer.

A recent Cochrane review of individual patient data from 13 randomised studies that compared palliative chemotherapy with best supportive care concluded that the use of chemotherapy was associated with a 3.7-month improvement in median survival.¹ This effect was consistent across all age groups. With respect to combination therapy, two randomised studies have demonstrated that the combination of 5-FU plus irinotecan results in superior survival compared to 5-FU alone as first-line treatment.^{2,3}

For patients not previously treated with irinotecan, the use of irinotecan as second-line therapy is associated with a significant survival advantage and a significant improvement in quality of life relative to best supportive care.^{4,5}

20.2 Timing of chemotherapy

Should chemotherapy be used when signs of advanced Colorectal Cancer first appear (early treatment), or should it wait until symptoms appear (delayed treatment)?

A study by the Nordic group enrolled 183 patients with asymptomatic metastatic Colorectal Cancer to receive either early or delayed 5-FU plus leucovorin.⁶ Early chemotherapy resulted in a greater symptom-free survival (median ten months compared to two months, $p < 0.001$) and the median survival was improved from nine to 14 months, but this was not statistically significant. Investigators from Australia and Canada recently reported on two almost identical randomised trials that also addressed the question of early versus delayed treatment.⁷ In a combined analysis of these two studies, which entered a total of 168 patients, no significant benefit in terms of quality of life or overall survival was evident from the use of early chemotherapy.

While a small but significant survival benefit has not been excluded by these studies, because they were only powered to detect very large difference in overall survival, they now have little relevance to current clinical practice where combination first-line regimens are now available, and second-line chemotherapy is standard.

20.3 Selection of chemotherapy

No single chemotherapy agent or combination regimen can be recommended as standard therapy for all patients presenting with metastatic Colorectal Cancer. Therapy therefore should be individualised, based upon previous treatment, disease extent, organ function, and medical comorbidities.

20.4 Chemotherapy options

20.4.1 Intravenous 5-FU-based chemotherapy

There is no standard method of delivering 5-FU chemotherapy. Options with intravenous 5-FU include bolus administration according to a variety of schedules (with or without leucovorin), and delivery as a continuous infusion. More recently, oral formulations have become available.

The value of adding leucovorin to 5-FU has recently been addressed in a meta-analysis of 18 studies with a total of 2751 patients.⁸ The addition of leucovorin significantly increased the response rate

(23% compared to 12%, $p < 0.0001$), and was associated with a small but statistically significant improvement in survival (one-year survival increased from 43% to 48% $p = 0.003$).⁸

Two standard regimens that combine 5-FU and leucovorin have been developed. The Mayo regimen of 5-FU 425 mg/m² plus leucovorin 20 mg/m² as an IV push is administered day 1–5 every four weeks. The Roswell Park regimen of 5-FU 500–600 mg/m² plus leucovorin 500 mg/m² over two hours is given weekly for 6 weeks, with courses repeated every eight weeks. A randomised study that compared these two regimens in 362 patients found similar response rates, palliative effects and survival outcomes.⁹ The Mayo regimen was associated with significantly more leucopenia and stomatitis, but less diarrhoea and fewer hospital admissions. The optimal dose of leucovorin is unclear. Randomised studies looking at low- versus high-dose leucovorin with the Mayo regimen of 5-FU found no significant difference in response rates or survival outcome^{10,11} Two similar studies, where the 5-FU was given according to a weekly schedule,^{12,13} reported increased response rates in the high-dose leucovorin arms, but survival endpoints were again unaltered, and toxicity and expense were increased.

Only one study has compared a weekly with a monthly 5-FU regimen using the same dose of leucovorin in each arm. Wang et al¹⁴ randomised 94 patients with previously untreated metastatic Colorectal Cancer to receive either weekly treatment (5-FU 400 mg/m² plus leucovorin 20mg/m²) or monthly treatment (5-FU 400mg/m² plus leucovorin 20mg/m² day 1–5). They reported that the response rate (14.3% vs. 10.6%, $p = \text{NS}$) and median survival (18.4 vs. 15.8 months, $p = \text{NS}$) was similar in both arms. However, the monthly arm produced higher rates of severe diarrhoea (14.9% vs. 2%, $p = 0.029$) and there was also a trend toward a higher rate of severe stomatitis (8.5% vs 0%, $p = 0.054$) with monthly treatment.

A potential advantage of weekly treatment is that it permits adjustment of dose if early signs of toxicity appear. When using a Mayo-type regimen, all five doses have typically been administered before significant toxicity is apparent.

The Meta-analysis Group in Cancer performed a review of studies comparing continuous infusion 5-FU with bolus administration. They reported a higher response rate (22% compared to 14%, $p = 0.0002$) and a slight survival benefit (12.1 compared to 11.3 months, $p = 0.04$) favouring infusional 5-FU.¹⁵ Bolus 5-FU was associated with more haematological toxicity, mainly neutropenia (31% compared to 4%, $p < 0.0001$), but less hand-foot syndrome (13% compared to 34%, $p < 0.0001$). A randomised study comparing a combination bolus/infusional 5-FU regimen (deGramont) versus bolus 5-FU alone has also recently been reported. The combination arm demonstrated an improved response rate (32.6% compared to 14.4%, $p = 0.0004$) and less grade 3 and 4 toxicity, but no significant difference in overall survival (median 62 compared to 56.8 weeks, $p = 0.067$).¹⁶ The disadvantage of infusional 5-FU delivery is the need for indwelling venous access and hence the potential for catheter-related complications.

20.4.2 Oral 5-FU-based chemotherapy

Until recently, the administration of fluoropyrimidines via the oral route was limited by unpredictable bioavailability. Now reliable drug delivery can be achieved by delivery as a prodrug (e.g. capecitabine), and/or in combination with an inhibitor of DPD (dihydropyrimidine dehydrogenase) that prevents GIT metabolism.¹⁷ A survey of 103 patients by Liu et al explored the patients' attitudes to oral therapy.¹⁸ Eighty-nine per cent preferred oral treatment due to the increased convenience of home administration and a preference for a pill rather than intravenous administration. However, 70% were not prepared to accept a lower response rate, indicating that from the patient perspective at least, therapeutic equivalence needs to be demonstrated with these agents.

The most mature and promising data is for capecitabine, a prodrug converted to the active form of 5-FU in the liver and tumour in a multi-step process. Pooled data from two studies that randomised previously untreated patients to receive either capecitabine or standard bolus 5-FU plus leucovorin

have recently been reported.¹⁹ Treatment with capecitabine was associated with a significantly greater response rate (25.7% compared to 16.7%) and significantly less toxicity, but there was no difference in survival endpoints. Capecitabine has a similar toxicity profile to infusional 5-FU.

UFT, a combination of a prodrug (ftorafur) and a DPD inhibitor (uracil), has also been extensively studied.¹⁷ Two randomised studies^{20,21} in patients with metastatic Colorectal Cancer, where UFT was compared to a standard 5-FU plus LV regimen, have demonstrated equivalence with respect to response rates, time to progression and overall survival. While UFT, like capecitabine,¹⁹ was associated with a significantly better safety profile, unlike capecitabine there was no improvement in response rate.

20.4.3 Raltitrexed

Raltitrexed, a direct thymidylate synthase inhibitor, has demonstrated equivalent activity to 5-FU plus leucovorin in patients with advanced disease.²² Raltitrexed is therefore considered an alternative treatment to 5-FU in certain circumstances, including patients experiencing unacceptable toxicity from 5-FU. This drug also has a more convenient schedule (once every three weeks), however this advantage is now less relevant due to the availability of oral 5-FU formulations. A major concern with raltitrexed is the high incidence of adverse events. In the setting of advanced disease, it was significantly more toxic than two 5-FU-based regimens (including an increase in treatment related deaths), and was associated with an inferior quality of life.²³ An adjuvant study of raltitrexed versus the Mayo regimen (PETACC-1) was terminated early due to unacceptable toxicity in the raltitrexed arm.

20.4.4 Irinotecan and oxaliplatin

Irinotecan (a topoisomerase I inhibitor) and oxaliplatin (a platinum analog) have significant single-agent activity in metastatic Colorectal Cancer.²⁴ These agents have also been widely studied in combination with 5-FU.

In two large randomised studies the combination of irinotecan and 5-FU achieved response rates significantly greater than those achieved with 5-FU alone (35% compared to 21% and 39% compared to 22%).²³ Overall survival was also improved (14.8 compared to 12.6 months, and 17.4 compared to 14.1 months). Two first-line studies of the combination of oxaliplatin plus 5-FU also demonstrated a superior response rate over 5-FU alone, (50% compared to 22% and 34% compared to 12%).^{25,26} However, in both studies there was no significant improvement in median survival. This may be because these studies were not powered to demonstrate significant differences in median survival and/or the use of second-line therapy was not controlled.

Early results from two studies that explored the optimal sequencing of irinotecan and oxaliplatin-based regimens have been reported. In a European study comparing first-line 5-FU plus irinotecan (FOLFIRI) followed by second-line 5-FU plus oxaliplatin (FOLFOX), or vice versa, response rate and survival data were almost identical for the two arms.²⁷ In a United States study of bolus 5-FU plus irinotecan (IFL) versus infusional 5-FU plus oxaliplatin (FOLFOX), an improved response rate and superior survival were reported for the patients initially treated with FOLFOX.²⁸ The FOLFOX regimen had a lower rate of nausea, vomiting, diarrhoea, febrile neutropenia and dehydration. Differences in the 5-FU schedules, and in second-line therapy (patients treated initially with IFL did not routinely receive second-line therapy with oxaliplatin) may account for the apparent superiority of the oxaliplatin-containing regimen as first-line treatment. In this study, the two-drug combination of irinotecan and oxaliplatin (IROX) was inferior to FOLFOX.

On current evidence, with no clearly superior regimen in terms of response rate or survival outcomes, a major consideration becomes the differing metabolism and toxicity profiles of these two agents. An exception may be patients with liver-only metastases that are initially considered inoperable. Preliminary evidence suggests that treatment with an oxaliplatin-containing regimen may result in

more patients having disease down-staged to the point of being surgically resected, although these data are somewhat subjective at present, and may be subject to considerable selection bias.²⁷ For patients with significantly impaired baseline liver function, where the pharmacokinetics of irinotecan are altered, dose adjustments are required.²⁹ Abnormal liver function or the presence of significant diarrhoea, which is likely to be exacerbated by irinotecan therapy, are therefore other reasons to favour an oxaliplatin-containing regimen as first-line therapy. For patients with an existing peripheral neuropathy, a common complication of oxaliplatin therapy, first-line treatment with irinotecan is favoured.

20.5 Second line and subsequent chemotherapy

The role of irinotecan alone after failure of initial 5-FU-based therapy has been addressed in two randomised studies. Irinotecan as a single agent was found to be significantly superior to either best supportive care,⁴ or an alternative schedule of 5-FU,⁵ in terms of survival duration and quality of life. The two commonly used irinotecan regimens (125 mg/m² day 1, 8, 15 and 22 of a 6-week cycle, and 350 mg/m² day 1 of a 3-week cycle) demonstrate similar efficacy and quality of life, but diarrhoea is significantly less with a 3-weekly schedule.³⁰

Where oxaliplatin is used as second-line treatment, it should be given in combination with 5-FU. This is based on the in-vitro synergy of these two agents and the apparently inferior response rates achieved with oxaliplatin alone.³¹ Data on oxaliplatin-containing regimens as second-line therapy is emerging. In a single-arm phase II trial of oxaliplatin in combination with 5-FU in 97 patients refractory to 5-FU alone, a response rate of 20.6% and median survival of 10.8 months were reported.³² An improved performance status was noted in 51% of patients on this study. In separate studies of patients previously treated with 5-FU plus irinotecan, response rates of 10% and 21% were achieved with a combination of oxaliplatin and 5-FU.^{27,31}

Given the proven impact of irinotecan as second-line therapy,^{4,5} and the limited data regarding oxaliplatin in this context, irinotecan should be considered the standard option for second-line treatment of patients initially treated with 5-FU alone.

20.6 Duration of chemotherapy treatment

Irrespective of the regimen chosen for first-line therapy, the optimal duration of treatment in those patients who achieve at least stable diseases and do not have unacceptable toxicity remains uncertain.

With respect to 5-FU-based regimens, a recent MRC study³³ suggests that routinely continuing therapy indefinitely may have an overall negative impact. In this study, 354 patients who had either partial response or stable disease after 12 weeks were randomised to continue therapy or to stop and then recommence at the time of progressive disease. Patients randomised to continue treatment ultimately received more treatment, experienced more toxicity and had an inferior quality of life without achieving an improvement in either progression-free or overall survival.

A recent study explored the optimal duration of second-line treatment with irinotecan. Patients who responded to treatment were randomised to discontinue treatment after a total of eight cycles of irinotecan 350-mg/m² q3w, or to continue until progressive disease. In this small study there was no clear benefit from continuing treatment.³⁴

20.7 Other treatment options for patients with metastatic Colorectal Cancer

20.7.1 Bevacizumab

Two recently-reported studies^{34,36} have demonstrated that agents targeting angiogenesis are likely to play a major role in the treatment of patients with metastatic Colorectal Cancer. In a study of 815

previously untreated patients, the addition of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, to standard chemotherapy resulted in a significant increase in response rate and overall survival.³⁵ In patients receiving IFL plus placebo, responses were seen in 35% of patients, in those receiving IFL plus bevacizumab, the response rate was 45% (p = 0.0029). The addition of bevacizumab also improved median survival from 15.6 months up to 20.3 months (p = 0.0003). There was an increased incidence of hypertension in the experimental arm but this was easily controlled with standard medication. Although uncommon, gastrointestinal perforation was limited to the bevacizumab arm. A combined analysis of three studies comparing bevacizumab plus 5-FU plus leucovorin with 5-FU plus leucovorin alone has been reported in abstract form and suggests a similar benefit.³⁶ However, the available data on the combination of 5-FU plus leucovorin plus bevacizumab in patients who have failed all standard chemotherapy options suggests that bevacizumab may provide little benefit in this context.³⁷

20.7.2 Cetuximab

Cetuximab is a chimeric anti-EGFR monoclonal antibody with efficacy against metastatic CRC previously resistant to treatment with irinotecan-based chemotherapy.³⁸⁻⁴² In this context, responses to the combination of cetuximab plus irinotecan were seen in about 23% of patients and to cetuximab alone in about 11% of patients with EGFR-positive tumours.³⁸⁻⁴¹ In the only randomised study,⁴² an impact on survival was not demonstrated, but cross-over was permitted for patients not initially randomised to receive cetuximab. No quality-of-life data are available. Further studies are required to define the role of this promising agent.

20.8 Quality of life

For patients with symptomatic metastatic Colorectal Cancer, an improvement in quality of life has been suggested with first-line 5-FU¹ and clearly demonstrated with second-line irinotecan.^{4,5} Preliminary results suggest that the use of 5-FU plus oxaliplatin in patients refractory to IFL results in significant relief of tumour-related symptoms, but the duration of benefit is short.³¹

Should chemotherapy be offered to patients with metastatic disease?

Guidelines — Systemic chemotherapy	Level of evidence	Practice recommendation	Refs
First-line FU-based chemotherapy prolongs life when compared to best supportive care and should be offered to patients with advanced Colorectal Cancer.	I	Strongly recommend	1

When is the optimal time to commence chemotherapy?

Guidelines — Systemic chemotherapy	Level of evidence	Practice recommendation	Refs
The optimal time to commence chemotherapy in patients who are initially asymptomatic is unclear.	II	Equivocal	6,7

What is the response rate in regimes of 5-FU chemotherapy?

Guidelines — Systemic chemotherapy	Level of evidence	Practice recommendation	Refs
After failure of 5-FU therapy, second-line treatment with irinotecan prolongs life and improves quality of life when compared to either best supportive care or an alternative regimen of 5-FU.	II	Recommend	4,5

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