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Future prospects for palliative care of mCRC

*Marc Ychou**

Centre Régional de Lutte contre le Cancer Val d'Aurelle, Montpellier, France

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ABSTRACT

The last two decades have seen a transformation in the management of metastatic colorectal cancer (mCRC), as first irinotecan and later oxaliplatin, capecitabine and the three approved targeted therapies have been added to 5-fluorouracil (5-FU) as options for treatment of this tumour. These developments have brought with them a significant improvement in outlook for many patients diagnosed with mCRC, as median overall survival (OS) has increased from approximately 12 months to over 2 years. With the continued high level of interest in searching for new drugs and regimens for improving the management of mCRC, as reflected in the large number of studies undertaken, further improvements can be expected in the near future. Doublet chemotherapy is now accepted as the standard of treatment for many patients. Studies are currently investigating the benefits of using combinations of three cytotoxic agents as well as exploring the impact that the addition of one or more targeted agents to combination chemotherapy can have on improving mCRC care. Promising results have already been reported in phase III studies, although further studies are required to determine the best regimens for particular settings. In addition to considering the clinical setting, it may also be relevant to consider tailoring therapy to the individual patient, based on the presence or absence of biomarkers predictive of response to a particular therapy. There is much interest in this approach and retrospective studies have identified a number of response markers to particular regimens. Prospective studies are required to further evaluate such markers and determine their possible value in the clinic. It can be hoped that such developments will help improve the outlook of many patients diagnosed with mCRC in the future.

1. Introduction

The last two decades have seen a transformation in the way metastatic colorectal cancer (mCRC) is treated. From the 1960s, when 5-fluorouracil (5-FU) was the only approved therapy, the diversity of treatment options has expanded greatly as an increasing number of therapies have gained approval.[1] In 1995, irinotecan monotherapy was approved as a treatment for mCRC in Europe; its use in combination with 5-FU was approved 4 years later. Oxaliplatin/5-FU combination therapy was granted a licence as a second-line therapy in 2002 and then as a first-line therapy in 2004.[1–3] Over the last 4 years further first- and second-line regimens such as bevacizumab/5-FU-based combination therapy, cetuximab in combination with irinotecan, and panitumumab monotherapy have been approved, all of which can be expected to improve the outlook for patients with mCRC.[1,2,4–6] In addition, capecitabine,

*Address for correspondence: M. Ychou. Centre Régional de Lutte contre le Cancer Val d'Aurelle, 208 Rue des Apothicaires, 34298, Montpellier Cedex 05, France.
Tel.: +33 (0) 4 6761 3066; fax: +33 (0) 4 6761 3022.
E-mail address: marc.ychou@valdorel.fnclcc.fr (M. Ychou).

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an oral fluoropyrimidine, was first marketed as a monotherapy for first-line use in 2001 and can be used in place of 5-FU in combination regimens. [7]

The number of recent drug approvals in this area reflects an ongoing drive to improve the treatment options and their outcomes for patients with mCRC. While much ongoing research is focussed on establishing the best ways of utilising the approved therapies at the various different stages in the treatment of mCRC, there is also much interest in further expanding the range of effective treatments and developing new approaches to the management of the disease. Important among these is the increasing use of neoadjuvant therapy in patients with unresectable liver metastases, aimed at shrinking the metastases to a size that enables resection. [8] Another area of active research is the use of biomarkers, which may have the potential to predict which patients are likely to respond to a particular therapy or whether a patient is at high risk of disease progression and thus might benefit from intensive therapy. [9] This paper reviews the results of ongoing research that may point the way to future developments in the management of mCRC.

2. Triple-agent combination chemotherapy

While fluoropyrimidine-based doublet regimens are becoming the standard treatment for mCRC, either in first- or second-line (as discussed in the preceding two papers of this supplement), ongoing research is investigating the benefit of the addition of further active agents. These include triple-chemotherapy regimens or chemotherapy plus one or more targeted agents.

Two recent phase III studies have reported the impact of combining all three approved cytotoxic agents (5-FU, oxaliplatin and irinotecan). In one study, the triple regimen FOLFOXIRI was found to significantly improve objective response rate (ORR; from 34% to 60%, $p < 0.001$), progression-free survival (PFS; 6.9 to 9.8 months, $p < 0.001$) and overall survival (OS; 16.7 to 23.6 months, $p = 0.042$) compared with 5-FU plus irinotecan (FOLFIRI) in previously untreated patients with unresectable mCRC ($n = 244$). [10] In addition, the percentage of patients who achieved an R0 resection of metastases increased from 6% to 15% ($p = 0.033$) for all patients and from 12% to 36% for patients with liver metastases alone ($p = 0.017$). The incidence of severe toxicities was greater in the triple-agent group, but adverse events were manageable. The results of this study therefore suggest that triple-agent chemotherapy could offer significant benefits over doublet chemotherapy in patients in whom therapy is tolerated.

The second study comparing FOLFOXIRI to FOLFIRI failed to report a significant benefit for the triple-agent regimen over doublet therapy, although time to progression (TTP; FOLFOXIRI, 8.4 months; FOLFIRI, 6.9 months), OS (FOLFOXIRI, 21.5 months; FOLFIRI, 19.5 months) and response rates (43% for FOLFOXIRI and 34% for FOLFIRI) were greater with the triple combination therapy. [11] This regimen involved slightly lower doses of each active agent, which may have contributed to the lack of benefit observed in this study. Despite the reduced dose, the triple-agent regimen was associated with a significantly higher incidence of alopecia, diarrhoea and neurosensory toxicity compared with FOLFIRI ($p \leqslant 0.001$).

A third, phase II, study has investigated the value of a triple-agent regimen, 5-FU/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX), given as neoadjuvant therapy in patients with liver metastases that were unresectable, but with the potential to become resectable following tumour reduction. [12] Of the 34 patients included in the study, 28 (82%) underwent hepatic resection after chemotherapy and nine (27%) achieved R0 resection. After surgery, 80% had complete remission and 2-year OS was 83%. Toxicities were manageable in most patients, with only four withdrawing due to toxicity. There were no toxic deaths.

Taken together, the results of these three studies suggest that triple-agent chemotherapy may have a role as first-line therapy in patients with mCRC, especially those for whom neoadjuvant therapy to reduce liver metastases may make resection feasible. However, the triple-agent regimen is associated with a significantly higher incidence of specific toxicities, namely diarrhoea, vomiting and neurosensory toxicity, the latter arising from the inclusion of oxaliplatin in the regimen. Further large scale phase III studies are therefore needed to assess the potential benefits and drawbacks of such an approach.

3. Capecitabine-based combination chemotherapy

Capecitabine has recently been approved in Europe for use in combinations with both oxaliplatin and irinotecan, either with or without bevacizumab, in first- and second-line mCRC treatment. The efficacy profile of these combinations is similar to that of the 5-FU-based regimens, although slight variations have been reported in the tolerability. [13–17]

The efficacy and tolerability of triple-agent chemotherapy with capecitabine (i.e. capecitabine, irinotecan and oxaliplatin) have also been investigated: two phase I dose-escalation studies have reported ORR of 79% and 71%, and PFS was 15 months in one study and had not been reached at 9.0 months in the second study. [18,19] Although these studies mainly enrolled patients with good performance status, so are likely to overestimate actual activity, the findings with this regimen are encouraging and warrant investigation in a phase II study.

Accumulating data indicate that capecitabine-based combination regimens have a similar efficacy to 5-FU-based regimens, although the safety profile differs

Table 1 – Studies investigating the addition of bevacizumab to fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin regimens

Study	Phase	No. of patients	Setting	Regimen to which bevacizumab added	ORR, %		PFS/TTP, months		OS, months	
					+B	−B	+B	−B	+B	−B
Fluoropyrimidine/irinotecan regimens										
Hurwitz 2004 [20]	Phase III	813	1st line	IFL	45	35	10.6	6.2, $p<0.001$	20.3	15.6, $p<0.001$
Kopetz 2007 [21]	Phase II	41	1st line	FOLFIRI	62		12.6			
Sobrero 2007 [22]	Phase IV	209	1st line	FOLFIRI	44		6-month PFS, 82%			
Kwon 2007 [23]	Pilot study	14	Refractory	FOLFIRI	29		3.9		10.9	
Fluoropyrimidine/oxaliplatin regimens										
NO16966 [24]	Phase III	1401	1st line	FOLFOX or CAPOX			9.4	8.0, $p=0.0023$		
ECOG3200 [25]	Phase III	829	Refractory	FOLFOX	33	9, $p<0.0001$	7.3	4.7, $p<0.0001$	12.9	10.8, $p<0.0011$

B, bevacizumab; IFL, bolus 5-FU/irinotecan.

somewhat. Further studies are required to confirm the additional value of capecitabine-based triple-agent regimens in the management of mCRC.

4. Adding targeted therapies to combination chemotherapy

An alternative option to adding a third cytotoxic agent to chemotherapy doublets is the addition of a targeted agent. Various studies have investigated the effects of adding bevacizumab, cetuximab or both to fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin regimens, as summarised in Tables 1 and 2.

4.1. *Bevacizumab*

The addition of bevacizumab to fluoropyrimidine in combination with irinotecan has been shown in several studies to lead to improvements in ORR, PFS and OS in the first-line setting. [16,20–22] Although improvements in responses are seen regardless of the specific regimen used for delivering 5-FU and irinotecan, greater survival benefits appear to be associated with infusional 5-FU (i.e. FOLFIRI). This is exemplified in the BICC-C study, where PFS data were 11.2 months and 8.3 months ($p=0.28$) and OS was 28.0 months and 19.2 months ($p=0.037$) for FOLFIRI and bevacizumab and mIFL plus bevacizumab, respectively. [16] A further study of this combination suggests that it also has activity in patients who have progressed after oxaliplatin- and irinotecan-based combination therapy. [23] In this pilot study involving 14 patients, 29% achieved objective responses and OS was 10.9 months.

The benefits of adding bevacizumab to FOLFOX have been demonstrated in two large phase III studies, one in newly-diagnosed patients [24] and one in previously-treated patients. [25] Both studies reported a significant increase in PFS for the addition of bevacizumab, and the study in previously-treated patients also reported a significant improvement in OS (see Table 1). In the study in newly-diagnosed patients (NO16966), patients received FOLFOX or capecitabine plus oxaliplatin (CAPOX), with or without bevacizumab. Statistically significant PFS improvement was achieved in the chemotherapy plus bevacizumab arm (9.4 months) compared with the chemotherapy plus placebo arm (8.0 months: $p=0.0023$, HR 0.83, 97.5% CI 0.72–0.95). This is consistent with the results from the TREE 2 study, which compared the efficacy of three oxaliplatin/fluoropyrimidine regimens (bolus, infusional, and oral) in combination with bevacizumab in first-line treatment of mCRC. In this study, adding bevacizumab to FOLFOX led to a small improvement in PFS (+1.2 months). [26] The difference in median OS between the bevacizumab and placebo arms did not reach statistical significance in the NO16966 study – 21.3 months in the chemotherapy plus bevacizumab arm and 19.9 months in the chemotherapy plus placebo arm ($p=0.0769$, HR 0.89, 97.5% CI 0.76–1.03). [24]

Taken together, these data suggest that the addition of bevacizumab to combination chemotherapy is a valuable option both in first-line and on disease progression. Further evaluation is needed to define the optimum stage to use bevacizumab in the treatment of the various different patient types.

4.2. *Cetuximab*

The combinations of cetuximab with irinotecan/fluoropyrimidine and oxaliplatin/fluoropyrimidine regimens have also been investigated in the first-line setting (see Table 2).

Table 2 – Studies investigating the addition of cetuximab to fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin regimens

Study	Phase	No. of patients	Setting	Regimen to which cetuximab added	ORR, %		PFS, months		OS, months	
					+C	−C	+C	−C	+C	−C
Fluoropyrimidine/irinotecan regimens										
Cunningham 2004 [27]	Phase III	329	Refractory	FOLFIRI	22.9	310.8 p = 0.007			8.6	6.9 p = NS
CRYSTAL [28]	Phase III	1217	1st line	FOLFIRI	47	39 p = 0.0038	8.9	8.0 p = 0.048		
Fluoropyrimidine/oxaliplatin regimens										
OPUS [29]	Phase II	337	1st line	FOLFOX4	46	36 p = 0.063	7.2	7.2		
Ocean 2007 [30]	Phase II	67	1st line	FOLFOX6 + bevacizumab	55		9.6		Not reached at 11.4 months	
CAIRO2 [31]	Phase III	755	1st line	Capecitabine/oxaliplatin + bevacizumab						

C, cetuximab.

Cetuximab showed significant activity alone and in combination with irinotecan (FOLFIRI) when used second-line in an open label, randomised, multi-centre trial. The ORR was significantly higher than in the monotherapy group: 22.9% versus 10.8% (p = 0.007). [27]

A larger study confirmed these findings. Adding cetuximab to FOLFIRI significantly improved response rates and PFS in a large phase III study – the CRYSTAL study – involving 1,217 patients. [28] In this study, the ORR was increased from 39% to 47% (p = 0.005) and PFS increased from 8.0 to 8.9 months (p = 0.036) with the addition of cetuximab, with improved responses being seen in the wild-type KRAS population.

A large, randomised phase II study of the addition of cetuximab to fluoropyrimidine/oxaliplatin in the first-line setting (OPUS; n = 337) has reported an increase in response rate for the addition of cetuximab (46% versus 36%). [29] The use of an additional targeted agent, bevacizumab, with this combination has also been investigated, with an ORR of 55% and PFS of 9.6 months being reported. [30] A third study is investigating the addition of cetuximab to CAPOX plus bevacizumab. [31] This large phase III study in previously untreated patients (n = 755) has reported that the addition of cetuximab does not increase gastrointestinal toxicity or treatment-related mortality. Efficacy data for this study have not yet been reported.

Recent reports, discussed in more detail below, have provided compelling support for the dependency of response to cetuximab on the patient's KRAS status. Further investigations are required to determine whether cetuximab is the first choice for first-line targeted therapy in KRAS wild-type patients, or whether there are advantages to reserving this therapy for later treatment stages.

4.3. Other targeted therapies

The addition of gefitinib or erlotinib to fluoropyrimidine/oxaliplatin regimens has also been investigated but studies to date suggest that this approach appears to confer no benefit. In a phase II study in which patients (n = 43) received FOLFOX4 plus gefitinib, an ORR of 35% was achieved, median PFS was 7.8 months and median OS was 13.9 months. [32] These data are similar to those achieved with FOLFOX4 alone. Two further studies have investigated the addition of erlotinib to FOLFOX/bevacizumab or CAPOX/bevacizumab. [33,34] Both studies reported that the addition of erlotinib was associated with an increase in toxicity but not with marked efficacy advantages, and hence suggest that this does not represent a likely treatment approach for mCRC in the near future.

5. New agents in development

The three targeted therapies approved for the treatment of mCRC all act via inhibiting signal transduction via specific growth factor receptors – vascular endothelial growth factor receptor (VEFG) in the case of bevacizumab and epidermal growth factor receptor (EGFR) for cetuximab and panitumumab. Two further agents in development also act via blocking signal transduction mediated by growth factor receptor tyrosine kinase activity. These are the EGFR tyrosine kinase inhibitor EKB-569 and vatalanib (PTK/ZK), which inhibits all VEGF receptors.

Two phase III studies have investigated the benefit of adding vatalanib to FOLFOX4 as first-line therapy (CONFIRM-1 trial) and as second-line therapy (CONFIRM-2). [35,36] Preliminary results from both studies indicate that the addition of vatalanib significantly improves PFS, especially in patients with high lactate dehydrogenase

(LDH) levels. EKB-569 has also been investigated when added to combination chemotherapy. Folprecht *et al.* have reported the results of a phase I dose-ranging study of EKB-569 in combination with FOLFIRI in previously untreated patients, where objective responses were achieved in 48% of patients and the time to progression (TTP) was 7.7 months. [37] A multi-targeted tyrosine kinase inhibitor that is already approved for use in renal cell carcinoma and GIST, sunitinib, has also shown promise when used in combination with FOLFIRI in treatment-naive patients in a phase I study. [38] Recruitment for a phase III study to explore the benefits of this combination in a larger mCRC population is ongoing. These results suggest that further agents that target growth factor receptors show promise for the management of mCRC in the near future.

Another approach being investigated that may increase the activity of 5-FU-based regimens is the addition of vorinostat, which decreases the expression of thymidilate synthase (TS). Since 5-FU acts by inhibiting TS, the addition of vorinostat can be expected to increase the antitumour activity of 5-FU. A phase I dose-ranging study has established the recommended dose of vorinostat when administered daily in combination with FOLFOX for 1 week followed by a break for 1 week, [39] although no objective responses were observed in this study. Alternative schedules of administration of vorinostat that might allow dose escalation may be warranted to investigate the value of this approach further.

There are also investigations ongoing in the use of monoclonal antibodies that target the A33 glycoprotein, a protein which is expressed specifically on intestinal epithelium and in most human colon cancers, but not on other normal tissues. A phase I study has investigated the safety and efficacy of a humanised anti-A33 monoclonal antibody, huA33, in combination with FOLFOX-4 in patients with mCRC. [40] The addition of huA33 did not alter the toxicity profile from that expected for FOLFOX-4 and objective responses were achieved in 38% of patients. Another phase I study is investigating the activity of radio-labelled huA33, 131-I-huA33, in combination with capecitabine. [41] One partial response has been reported and 8 patients achieved stable disease (disease control rate, 64%).

Results to date indicate that use of therapies designed to inhibit specific biomolecular targets could enhance the control of CRC, but further studies are required to establish the true value of these agents, and their optimal place in the management of this disease.

6. Genetic markers for response to therapy

With the continuing increase in the number of treatment options and the potential combinations of these therapies, there is a greater need to optimise the approach to treatment and try to predict the response of a patient to a particular therapy. This would allow therapy to be tailored to the individual patient, meaning that not only could specific therapies be given to those patients most likely to respond, but patients at lower risk of disease progression could also be spared unnecessary intensive therapies.

It would be expected that agents targeted towards specific genes would have their efficacy determined by the levels of those genes or the presence of mutations. For this reason, cetuximab is licensed for use in EGFR-positive CRC only. On-going research is exploring the potential of additional markers to aid in identifying those patients either with the greatest chance of response or at greater risk of poor tolerability.

A number of recent studies have aimed to identify possible markers of response to cetuximab. For example, Finocchiaro *et al.* analysed gene copy number for EGFR, HER2 and the presence of KRAS mutations in tumours from 85 CRC patients treated with cetuximab. [42] Increased EGFR gene copy number was associated with a greater chance of response and longer TTP, while patients having KRAS mutations were least likely to benefit from cetuximab, as were patients with increased HER2 gene copy number. The influence of KRAS status on response to EGFR inhibitors has also been confirmed in a number of large studies, such as CRYSTAL and OPUS, with median PFS found to be approximately 2 months greater in the wild-type patients. [28,29] Another study reported that specific germline polymorphisms were predictive for clinical outcome for patients with mCRC treated with irinotecan/bevacizumab/cetuximab or irinotecan/bevacizumab, [43] while the results of a further trial suggest that levels of expression of particular genes (e.g. EGFR and VEGFR2) may be used as predictors of response to these combinations. [44]

Genetic polymorphisms have also been shown to have predictive value for responses to FOLFOX [45] and FOLFOX/bevacizumab or CAPOX/bevacizumab. [46] For example, Ruzzo *et al.* [45] identified three genotypes that were independently associated with an adverse PFS and a further genotype associated with a greater risk of severe neurotoxicity.

It should also be remembered that, in addition to the targeted agents, biomarkers that could aid in improving the use of chemotherapy may also exist. For example, Seymour *et al.* have suggested the use of the marker topoisomerase-1 may aid in discerning those patients likely to benefit from combination therapy rather than a planned sequential approach. [47]

Accumulating results from such analyses suggest that genetic markers may be a valuable method in predicting response to treatment. However, prospective studies using such markers are required to validate these findings, and it is necessary to consider whether such an approach is practical in the clinical setting. Further

research is required to determine which markers are likely to be most valuable across the range of patients with mCRC.

7. Conclusions

Promising data emerging from recent studies suggest that treatment options for mCRC are likely to become more complex in the future. While two-agent combination chemotherapy is now widely accepted as standard treatment for many patients, further treatments are now being added to these regimens. However, the relative benefits of adding a third cytotoxic compared with a targeted agent have yet to be investigated, as have differences between the available targeted agents. Further therapies with a variety of molecular targets are also in development, and may well increase the treatment options for mCRC in the near future.

In order to make best use of the rapidly-growing range of active agents against mCRC, it may be helpful to identify biomarkers that are predictive for response to a particular therapy. There is growing interest in this approach and retrospective analysis of data from patients treated with various regimens is helping identify genetic markers of response to particular regimens. Prospective evaluation of such markers is now warranted to confirm their value and help determine the most appropriate markers for clinical use.

With so much active research into new treatments and approaches to the management of mCRC, the outlook for patients with mCRC in the near future looks promising. Developments over the past decade have increased the median OS for such patients from approximately 1 year to over 2 years. Hopefully, the next decade will see further improvements in OS and quality of life for the many patients diagnosed with mCRC.

Conflicts of interest statement

Professor Ychou has been as advisor for Pfizer, Roche, Merck and Amgen.

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