Therapeutic strategy in unresectable metastatic colorectal cancer

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Abstract: While surgery is the cornerstone treatment for early-stage colorectal cancer, chemotherapy is the first treatment option for metastatic disease when tumor lesions are frequently not fully resectable at presentation. Mortality from colon cancer has decreased over the past 30 years, but there is still a huge heterogeneity in survival rates that can be mainly explained by patient and tumor characteristics, host response factors, and treatment modalities. The management of unresectable metastatic colorectal cancer is a global treatment strategy, which applies several lines of therapy, salvage surgery, maintenance, and treatment-free intervals. The individualization of cancer treatment is based on the evaluation of prognostic factors for survival (serum lactate dehydrogenase level, performance status), and predictive factors for treatment efficacy [Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation status]. The available treatment modalities for metastatic colorectal cancer are chemotherapy (fluoropyrimidine, oxaliplatin, irinotecan), anti-angiogenic agents (e.g. bevacizumab), and anti-epidermal growth factor agents (cetuximab, panitumumab). The increasing number of active compounds dictates the strategy of trials evaluating these treatments either in combination or sequentially. Alternative outcomes that can be measured earlier than overall survival are needed to shorten the duration and reduce the size and cost of clinical trials.

Keywords: chemotherapy, clinical trial, colorectal cancer, molecular targeted therapy

Introduction

Colorectal cancer is the third most common cancer and the third cause of cancer death in western countries [Globocan, 2008]. The main parameter to predict survival or relapse is tumor staging [American Cancer Society, 2010]. While surgery is the cornerstone treatment for early-stage cancer (stage I–III), chemotherapy is the first treatment option for metastatic disease (stage IV) when tumor lesions are frequently not fully resectable at presentation. Approximately one third of patients with metastatic colorectal cancer (MCRC) have metachronous disease, which is currently defined as more than 1 year between the occurrence of the primitive tumor and metastasis. Mortality from colon cancer has decreased over the past 30 years, partly due to better treatment modalities. Heterogeneity in survival rates can be mainly explained by patient and tumor characteristics, host response factors, and treatment strategy (drugs, regimen, and surgery of metastasis).

This review focuses on the management of unresectable MCRC. Trial acronyms are used for brevity: readers may refer to the cited references for full study names and details.

Prognostic factors

Several parameters have been found to be independent prognostic factors for MCRC. These are patient characteristics such as World Health Organization (WHO) performance status (PS), age, sex, weight loss, biological variables such as white blood cell (WBC) count, serum alkaline phosphatase (ALP) level, serum lactate dehydrogenase (LDH) level, serum carcino-embryonic antigen (CEA) level, or tumor characteristics like the number of metastatic sites, or liver involvement.

Three risk groups for death were recognized in patients receiving 5-fluorouracil (5-FU)-based chemotherapy for MCRC, depending on four

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baseline prognostic parameters: PS, WBC count, ALP, and number of metastatic sites [Köhne *et al.* 2002].

The Groupe Coopérateur Multidisciplinaire en Oncologie (France) (GERCOR) prognostic score was recently developed and validated in patients treated with oxaliplatin- or irinotecan-based chemotherapy. This model was based on the two most important prognostic factors, LDH level and WHO PS, before starting first-line chemotherapy. The median survival in patients having PS0 and normal LDH value was twofold higher than in patients with poor prognosis (PS1 and LDH>1N, or PS2) [Chibaudel *et al.* 2011b].

Antitumor drugs

Chemotherapy

Three cytotoxic drugs are available for the treatment of MCRC: fluoropyrimidines, oxaliplatin, and irinotecan. These drugs can be administered either in combination (doublets: fluoropyrimidine/oxaliplatin [de Gramont *et al.* 2000; Goldberg *et al.* 2006; Diaz-Rubio *et al.* 2007], 5-FU/irinotecan [Tournigand *et al.* 2004; Douillard *et al.* 2000; Fuchs *et al.* 2007]; triplet: 5-FU/oxaliplatin/irinotecan [Falcone *et al.* 2007]); or as monotherapy (fluoropyrimidine alone) [de Gramont *et al.* 1997; Van Cutsem *et al.* 2001].

Molecular-targeted agents

Anti-angiogenic agents. Angiogenesis, the formation of new blood vessels, takes part in tumor cell proliferation and thus is a target for antitumor therapy. Vascular endothelial growth factor (VEGF), a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiological and pathological angiogenesis. Increased levels of VEGF expression have been found in most human malignancies.

Bevacizumab (Avastin, Roche, Bale, Switzerland) is a recombinant humanized monoclonal immunoglobulin G1 antibody targeting VEGF. Adding bevacizumab to commonly used chemotherapy regimens improves outcomes in patients with MCRC. Infrequent specific bevacizumab-related side effects are bleeding, hypertension, fistulae, gastrointestinal perforation, arterial thromboembolic events, and proteinuria. The occurrence of hypertension and proteinuria is likely to be dose

dependent. A reversible posterior leukoencephalopathy syndrome has been reported in rare cases.

Aflibercept (Zaltrap, Sanofi-Aventis, Paris, France; Regeneron, Tarrytown, NY) is an investigational (i.e. it has not been approved by the US Food and Drug Administration) fusion protein for the treatment of cancer (colorectal, lung, prostate) and wet macular degeneration. This drug is designed to bind to circulating VEGF-A, VEGF-B, and placental growth factor in the bloodstream and in the extravascular space with higher affinity than their native receptors.

Anti-epidermal growth factor agents. Cetuximab (Erbix, Merck, Darmstadt, Germany) is a chimeric human mouse anti-epidermal growth factor receptor (EGFR) monoclonal antibody. Panitumumab (Vectibix, Amgen, Thousand Oaks, CA) is a fully human anti-EGFR monoclonal antibody. These two drugs have been studied as monotherapy and in combination with oxaliplatin- or irinotecan-based therapy in a palliative setting. It has been shown that only patients with wild-type Kirsten rat sarcoma viral oncogene homolog (KRAS) tumors respond to anti-EGF agents and have a prolongation of progression-free survival (PFS) [Lièvre *et al.* 2008]. Thus, the KRAS tumor gene has been validated as a negative predictive marker for anti-EGF agent activity, but additional testing for tumor genes such as serine/threonine-protein kinase B-Raf (BRAF) or neuroblastoma N-Ras (NRAS) could be useful to identify patients who might benefit the most from anti-EGF agents [Di Nicolantonio *et al.* 2008; Laurent-Puig *et al.* 2009; Khambata-Ford *et al.* 2007]. In contrast to anti-angiogenic agents, the benefit of anti-EGF agents is maintained or even amplified in second- or third-line therapy when a survival benefit is observed. This suggests that if the goal is survival, it might be better to use anti-EGF drugs as salvage therapy.

First-line therapy

Irinotecan- or oxaliplatin-based regimens as first-line chemotherapy?

The choice of oxaliplatin- or irinotecan-based regimens is a matter of debate. The C97-3 study was the first direct comparison between the addition of oxaliplatin or irinotecan with a simplified leucovorin/5-FU (LV5FU2) regimen [Tournigand *et al.* 2004]. The final results did

not show any difference between FOLFIRI (leucovorin/5-FU/irinotecan regimen) and FOLFOX6 (leucovorin/5-FU/oxaliplatin regimen) in first-line therapy in terms of response rate (RR 54% and 56%) and PFS (8.4 and 8.0 months). These results were confirmed in another trial [Colucci *et al.* 2005]. The main difference between these two combinations is mainly in the toxicity profile. Grade 3–4 gastrointestinal toxicities (nausea, vomiting, mucitis) and alopecia were significantly more frequent with the FOLFIRI regimen, whereas grade 3–4 neutropenia and neuropathy were significantly more frequent with the FOLFOX regimen.

Arguments favoring FOLFIRI first line were less grade 3–4 toxicity and better activity of FOLFOX second line (RR 15% *versus* 4%; PFS 4.9 *versus* 2.3 months) while arguments in favor of FOLFOX first line were fewer patients with serious adverse events, more patients amenable to surgery of metastases, and fewer chemotherapy cycles to achieve the same results. The main reason for stopping oxaliplatin was the cumulative drug neurosensory toxicity in patients free of progression. Thus, the potential of FOLFOX could be improved by the management of oxaliplatin-induced neuropathy. Moreover, the difference in the incidence of grade 3–4 toxicity is due to neutropenia, which in most cases is not clinically relevant.

Anti-angiogenic agents or anti-epidermal growth factor agents in combination as first-line chemotherapy?

Anti-angiogenic agents as first-line therapy. The addition of bevacizumab to oxaliplatin-based (N016966) or irinotecan-based (AVF2107g) chemotherapy improved survival [Saltz *et al.* 2008; Hurwitz *et al.* 2004]. Of note, this improvement was effective in wild-type and mutated KRAS MCRC [Rosen *et al.* 2008]. Thus, KRAS testing is not warranted in the selection of patients for bevacizumab-based therapy in MCRC. The magnitude of benefit was higher with irinotecan [hazard ratio (HR) = 0.54] than with oxaliplatin (HR = 0.83). This might be due to a better synergy between irinotecan and bevacizumab, or to more prolonged administration of bevacizumab in the irinotecan trial (AVF2107g). In the oxaliplatin-based trial (N016966), a large proportion of patients stopped treatment earlier than allowed by the study protocol. The treatment was discontinued because of progression in only 29% of

patients in the bevacizumab-containing arms and in 47% of patients in the placebo-containing arms. The benefit of bevacizumab was larger in the predefined on-treatment PFS analysis (HR = 0.63): if events occurred more than 28 days after stopping study medication, the patient was censored back to the date of last known nonprogression.

Adding bevacizumab to fluoropyrimidine alone also achieved a highly significant improvement in PFS. The AVF2192g study provided further support for combination with 5-FU/ leucovorin, although the patient population was different than that for the AVF2107g study (only patients who were not candidates for first-line irinotecan treatment were eligible for the trial) [Kabbavar *et al.* 2005]. Median PFS was increased from 5.5 to 9.2 months (HR = 0.50), and median overall survival (OS) was increased from 12.9 to 16.6 months (HR = 0.79). In the MAX study, bevacizumab was added to capecitabine [Tebbutt *et al.* 2010]. Median PFS was increased from 5.7 to 8.5 months (HR = 0.63), but median OS was similar in the two treatment groups (HR = 0.87).

Vatalanib and cediranib, two recent oral VEGF receptor-2 (KDR) tyrosine kinase inhibitors (TKIs), have been evaluated in first-line MCRC therapy. In the CONFIRM1 trial, 1168 patients with previously untreated MCRC were randomly assigned to receive FOLFOX4 plus vatalanib or placebo [Hecht *et al.* 2011]. Response rate, PFS (HR = 0.88), and OS (HR = 1.08) were not improved with vatalanib in the whole population. Of note, PFS was longer with vatalanib in patients with high serum LDH level at baseline (HR = 0.67) [Schmoll *et al.* 2010]. In the HORIZON III study (1422 patients), the direct comparison of cediranib and bevacizumab in combination with a modified FOLFOX6 regimen did not show any difference between the two regimens in terms of efficacy (RR, odds ratio = 0.96; HR_{PFS} = 1.10; HR_{OS} = 0.94). Moreover, the bevacizumab-based therapy had a more favorable toxicity profile with less severe diarrhea and neutropenia.

Anti-epidermal growth factor agents as first-line therapy. In patients with KRAS wild-type tumors, the addition of cetuximab to either FOLFIRI (CRYSTAL) or FOLFOX (OPUS) produced an improvement in median PFS (HR = 0.68 and 0.54) [Van Cutsem *et al.* 2009; Bokemeyer *et al.* 2009]. Similarly, the addition of panitumumab to FOLFOX (PRIME) was superior to

Table 1. Randomized trials in metastatic colorectal cancer first-line therapy: results in a wild-type KRAS population.

Study	E	Regimen	N	KRAS testing (%)	RR (%) (Δ)	PFS (months)	OS (months)
<i>Bev trials</i>							
AVF2107g (Hurwitz et al., 2004)	OS	IFL $\pm$ bev	67/85	28	37/60 (+23%)	7.4/13.5 (HR = 0.44)	17.6/22.7 (HR = 0.58)
PACCE (Hecht et al., 2008)	PFS	Oxali based + bev	203	82	56	12.5	19.8
CAIRO2 (Tol et al., 2009)	PFS	Irinotecan based	58		48	13.5	27.7
		XELOX + bev	156	71	50	10.6	22.4
<i>EGF trials</i>							
CRYSTAL (Van Cutsem et al., 2009)	PFS	FOLFIRI $\pm$ CTX	350/316	89	40/57 (+17%)	8.4/9.9 (HR = 0.70)	20.0/23.5 (HR = 0.80)
OPUS (Bokemeyer et al., 2009)	RR	FOLFOX $\pm$ CTX	73/61	69	37/61 (+24%)	7.2/7.7 (HR = 0.57)	18.5/22.8 (HR = 0.85)
PRIME (Douillard et al., 2010)	PFS	FOLFOX $\pm$ Pmab	331/325	93	48/55 (+7%)	8.0/9.6 (HR = 0.80)	19.7/23.9 (HR = 0.83)
COIN (Maughan et al., 2011)	OS	Oxali based $\pm$ CTX	367/362	81	57/64 (+7%)	8.6/8.6 (HR = 0.96)	17.9/17.0 (HR = 1.38)
NORDIC VII (Tveit et al., 2011)	PFS	FLOX $\pm$ CTX	97/97	88	47/46 (–1%)	8.7/7.9 (HR = 1.07)	22.0/20.1 (HR = 1.14)
bev, bevacizumab; CTX, cetuximab; E, primary endpoint; EGF, epidermal growth factor; HR, hazard ratio; KRAS, Kirsten rat sarcoma viral oncogene homolog; N, number of patients; OS, overall survival; PFS, progression-free survival; Pmab, panitumumab; RR, response rate.							

FOLFOX alone in terms of PFS (HR = 0.83) [Douillard *et al.* 2010]. In this study, the improvement in OS was not statistically significant (HR = 0.83; $p = 0.07$). The only significant improvement in OS (median increased by 3.5 months) in a first-line trial has been reported in the CRYSTAL trial. Unfortunately, the positive results came from a retrospective analysis and the proportion of patients who received cetuximab after first line in the control arm was not reported. A limited number of crossover patients (cetuximab in second or third line) in the control arm may explain this survival advantage for cetuximab in first-line therapy (Table 1).

Two first-line phase III trials contrasted with these results [Maughan *et al.* 2011; Tveit *et al.* 2011]. In the COIN trial, 1630 patients were randomized to receive either oxaliplatin-based chemotherapy [FOLFOX or XELOX (capecitabine plus oxaliplatin regimen)] alone or in combination with cetuximab. A third arm received intermittent chemotherapy. In the NORDIC VII trial, 571 patients were randomized to receive either continuous FLOX

(leucovorin/5-FU/oxaliplatin regimen) until progression or limiting toxicity, or the same chemotherapy in combination with cetuximab. A third arm received intermittent FLOX chemotherapy with continuous cetuximab. In these two trials, PFS and OS did not differ among treatment groups in patients with wild-type KRAS tumors (COIN: HR_{PFS} = 0.96, HR_{OS} = 1.04; NORDIC VII: HR_{PFS} = 1.07; HR_{OS} = 1.14). Unexpectedly the KRAS status did not affect the efficacy of cetuximab in the NORDIC VII trial. Of note, cetuximab did not improve PFS and OS, even in patients with wild-type KRAS tumor.

Based on these data, it is too early to recommend the systematic use of an anti-EGFR antibody in combination with oxaliplatin as first-line therapy in patients with wild-type KRAS unresectable metastases.

The addition of both an anti-angiogenic agent and an anti-EGF agent to chemotherapy had a negative impact on survival in comparison to chemotherapy with bevacizumab [Hecht *et al.* 2008; Tol *et al.* 2009].

Second-line therapy

Most patients should be offered second-line therapy when tumor progression or unacceptable toxicity stops first-line therapy. Effective second-line therapies are available. Knowledge of the most active second-line regimens must not lead to using a suboptimal first-line regimen. It has been reported that exposure to all available agents could be more important than the number of lines [Grothey *et al.* 2004]. However, based on the correlation between the percentage of patients who received all the available drugs and median survival, if all eligible patients receive all the drugs, the median survival would still be limited to 22 months. New strategies using targeted agents or the oxaliplatin stop-and-go strategy have already achieved median survival well over 22 months and argue against this basic approach. In the C97-3 study, the FOLFIRI regimen was less active in second-line therapy in patients whose condition failed to respond to FOLFOX6 than FOLFOX6 after progression on FOLFIRI. Of note, more than 70% of patients received second-line therapy and 13% of patients had R0 surgery of metastases on FOLFOX and 7% on FOLFIRI.

Second-line therapy after oxaliplatin-based first-line chemotherapy

Chemotherapy regimen. Irinotecan-based chemotherapy is the treatment of choice after oxaliplatin-based therapy failure. The expected overall response rate and median PFS of the standard FOLFIRI regimen are 4–12% and 2.5–4.7 months, respectively [Tournigand *et al.* 2004; Van Cutsem *et al.* 2011; Peeters *et al.* 2010]. This regimen was enhanced based on a positive interaction between irinotecan and 5-FU given after 5-FU infusion [Inoue *et al.* 2006]. Indeed, the FOLFIRI3 regimen has shown a RR of 20–25% and a median PFS of 3.7–4.7 months without any targeted agents in several studies [Mabro *et al.* 2006; Bidard *et al.* 2009]. However, these results have not been evaluated in randomized trials.

Anti-angiogenic agents. In the EFC10262-VELOUR trial, the addition of aflibercept to the standard FOLFIRI regimen was evaluated in 1226 patients after failure of oxaliplatin-based chemotherapy. The new combination significantly improved both PFS (4.7–6.9 months, HR = 0.76) and OS (12.1–13.5 months, HR = 0.82). This effect was seen whether or not patients had received prior bevacizumab therapy [Van Cutsem *et al.* 2011].

Anti-epidermal growth factor agents. In the EPIC trial, cetuximab added to irinotecan after 5-FU/oxaliplatin failure significantly improved PFS (4.0 *versus* 2.6 months; HR = 0.70) and RR (16.4% *versus* 4.2%) [Sobrero *et al.* 2008]. The absence of survival advantage can be partly due to crossover: half of the control patients received cetuximab as post-trial therapy. KRAS mutation status was retrospectively obtained for only 23% of randomized patients. In the small subset of patients with wild-type KRAS tumor (15% of the whole population), PFS was longer when cetuximab was added to irinotecan, but RR and OS were similar. [Langer *et al.* 2008]. The combination of panitumumab and FOLFIRI (181 study) was superior to the same chemotherapy in terms of RR and PFS, but not OS [Peeters *et al.* 2010]. The magnitude of the PFS benefit remains modest and consistently below 3 months. One acceptable hypothesis to explain the discrepancy between PFS and OS is crossover in the chemotherapy-alone arms.

Second-line therapy after irinotecan-based first-line chemotherapy

Chemotherapy regimen. An oxaliplatin-based chemotherapy regimen is the cornerstone treatment after failure of an irinotecan-based therapy. The expected overall RR and median PFS with FOLFOX as second-line therapy are 9–15% and 4.2–4.7 months, respectively [Tournigand *et al.* 2004; Giantonio *et al.* 2007].

Anti-angiogenic agents. The addition of bevacizumab to FOLFOX (E3200) after 5-FU/irinotecan failure led to an improvement in RR, PFS (4.7–7.3 months, HR = 0.61), and OS (10.8–12.9 months, HR = 0.75) [Giantonio *et al.* 2007]. Continuing bevacizumab after progression on first-line therapy may also prolong survival and is being evaluated in prospective trials [Grothey *et al.* 2008]. In the CONFIRM2 trial (855 patients), vatalanib in combination with FOLFOX after 5-FU/irinotecan failure has demonstrated significant prolongation of PFS (4.1–5.5 months, HR = 0.83) but not OS (HR = 0.94) [Köhne *et al.* 2007].

Anti-epidermal growth factor agents. No data from phase III trials are available for anti-EGF agents in this setting.

Finally, a benefit in OS in second-line therapy was observed only in trials using an anti-angiogenic agent in combination with FOLFIRI or FOLFOX [Van Cutsem *et al.* 2011; Giantonio *et al.* 2007].

Third-line therapy

After exposure to oxaliplatin- and irinotecan-based treatment, a significant number of patients are still able and willing to receive therapy.

The BOND trial, in which a significant proportion of patients were not only refractory to irinotecan-based chemotherapy but also to oxaliplatin-based chemotherapy, demonstrated a synergy between irinotecan and cetuximab [Cunningham *et al.* 2004]. The response rate for irinotecan plus cetuximab was superior to the response rate for the monoclonal antibody alone (23% *versus* 11%), and the HR for disease progression in the combination therapy group compared with the monotherapy group was 0.54 (median PFS 4.1 *versus* 1.5 months). Later studies demonstrated that the anti-EGFR monoclonal antibodies cetuximab and panitumumab were also active alone as third-line treatment *versus* best supportive care, and the results were amplified in the wild-type KRAS population [Jonker *et al.* 2007; Van Cutsem *et al.* 2007]. Thus, there is an unquestionable survival advantage for anti-EGFR monoclonal antibodies in third-line therapy in the wild-type KRAS population.

Knowing that bevacizumab is not active in third-line therapy [Chen *et al.* 2006; Kang *et al.* 2009] the only active third-line therapies are based on anti-EGFR monoclonal antibodies, which are only active in wild-type KRAS tumors. Consequently, there is no standard third-line therapy for patients with mutated KRAS tumors and for patients with wild-type KRAS tumors who receive anti-EGFR treatment as first- or second-line therapy.

Strategies

To date, treatment until progression or unacceptable toxicity, and allowing the administration of all available drugs sequentially or in combination has been the standard practice for advanced colorectal cancer. Various treatment strategies are depicted in Figures 1 and 2.

Stop-and-go strategy

Stop-and-go strategies especially fit with therapies inducing cumulative toxicity, such as oxaliplatin, which have to be stopped before disease progression. In cases of reversible toxicity (e.g. sensory neuropathy) reintroduction of the same therapy can be proposed at progression.

The concept of maintenance therapy with fluoropyrimidine alone, referred to as oxaliplatin stop-and-go strategy [de Gramont, 2008], was evaluated in the OPTIMOX1 study, in which 620 patients with unresectable MCRC were randomized to either FOLFOX4 until progression or the oxaliplatin stop-and-go strategy [Tournigand *et al.* 2006]. This strategy consisted of six cycles of FOLFOX7 chemotherapy [Maindrault-Goebel *et al.* 2001] followed by maintenance therapy with the simplified LV5FU2 regimen without oxaliplatin. After 12 cycles of LV5FU2 chemotherapy, FOLFOX7 was reintroduced in patients with controlled disease. This study demonstrated that a short induction with oxaliplatin followed by maintenance therapy with 5-FU alone was better tolerated than and achieved a similar efficacy as continuous administration of the drug until progression or the occurrence of cumulative neurotoxicity.

Maintenance therapy with fluoropyrimidine and bevacizumab was evaluated in the Combined Oxaliplatin Neuropathy Prevention Trial (CONcePT). This trial compared continuous administration of FOLFOX with intermittent administration of eight cycles of FOLFOX plus bevacizumab followed by eight cycles of maintenance LV5FU plus bevacizumab, and FOLFOX reintroduction plus bevacizumab for eight cycles [Grothey *et al.* 2008]. PFS with continuous administration was 7.3 months compared with 12.0 months with the stop-and-go strategy.

Maintenance therapy with targeted agents

Recent studies have evaluated maintenance therapy without chemotherapy. Targeted therapies blocking a critical pathway for tumor growth can delay tumor progression with fewer side effects than chemotherapy.

Maintenance therapy with cetuximab alone. Maintenance therapy with cetuximab alone was evaluated in the NORDIC VII study [Tveit *et al.* 2011]. OS for patients treated with continuous cetuximab and a chemotherapy-free interval (FLOX) was similar to that for patients with continuous chemotherapy (FLOX) with or without cetuximab.

Maintenance therapy with bevacizumab alone. Maintenance therapy with bevacizumab alone was compared with continuous XELOX plus bevacizumab therapy in the Spanish MACRO trial [Tabernero *et al.* 2010]. The primary endpoint was median PFS with a noninferiority limit of

Figure 1. Examples of treatment strategies for metastatic colorectal cancer. CFI, chemotherapy-free interval; chemo, chemotherapy; PD, progression disease.

7.6 months (i.e. HR = 1.32), assuming 10 months as median PFS in the control arm. Median PFS was 10.4 months in the continuous arm (control) and 9.7 months in the maintenance arm (investigational), with a HR of 1.11 (0.89–1.37). The authors concluded that noninferiority was not strictly demonstrated, but a detriment in PFS of more than 3 weeks could be excluded. Moreover, there was no statistically significant difference in OS (22.4 *versus* 21.7 months) between the two groups (HR = 1.04).

Maintenance therapy with double pathway inhibition. In the ACT-1 study, 159 patients were randomized to receive either maintenance therapy with bevacizumab alone or a combination of bevacizumab and erlotinib, an oral EGFR TKI, after 4.5 months of oxaliplatin- or irinotecan-based induction chemotherapy with bevacizumab (investigator's discretion). There was a trend for longer maintenance PFS in the combination arm

(4.2–5.9 months, HR = 0.81; $p = 0.24$), but this study lacked sufficient statistical power to detect the effects of interest [Johnson *et al.* 2011].

Treatment-free interval

The evolution of treatment for colorectal carcinoma resulted in approximately 12 months of median OS with 5-FU alone, 20 months in the oxaliplatin and irinotecan era, and more than 20 months when patients were exposed to all available drugs. Chemotherapy-free intervals (CFIs) are frequently used in patients with advanced colorectal cancer, for several reasons, including lengthy sustained responses or stabilization, toxicity, and the patient's decision to discontinue treatment. The gradual prolongation of median survival in patients with metastatic disease and the difficulty in keeping patients on therapy for a long time have led to the evaluation of chemotherapy discontinuation in prospective trials.

Figure 2. Treatment options in unresectable wild-type Kirsten rat sarcoma viral oncogene homolog (KRAS) metastatic colorectal cancer.

CT, chemotherapy; EGF, epidermal growth factor. Study acronyms are used for brevity: readers may refer to the cited references in the text for full details of study names and details. OPTIMOX (Tournigand *et al.*, 2006); CONcePT (Grothey *et al.*, 2008); AVF2107g (Hurwitz *et al.*, 2004); PRIME (Douillard *et al.*, 2010); CRYSTAL (Van Cutsem *et al.*, 2009); 181 (Peeters *et al.*, 2010); FOLFIRI3 (Mabro *et al.*, 2006); E3200 (Giantonio *et al.*, 2007); BRITE (Grothey *et al.*, 2008); VELOUR (Van Cutsem *et al.*, 2011); BOND (Cunningham *et al.*, 2004).

Two recent studies evaluated completely stopping therapy in patients receiving combination chemotherapy. The OPTIMOX2 study compared the oxaliplatin stop-and-go strategy with completely stopping chemotherapy after 3 months of induction FOLFOX7 chemotherapy in the first-line treatment of MCRC [Chibaudel *et al.* 2009]. The results were in favor of maintenance therapy. The median duration of disease control (DDC), the primary endpoint, was significantly longer in the maintenance arm than in the CFI arm (13.1 *versus* 9.2 months, HR = 0.71). Median PFS and median OS were also longer in the maintenance arm. The MRC COIN study (815 patients per arm) compared continuous oxaliplatin-based chemotherapy until disease progression with a complete stop-and-go strategy after 3 months of oxaliplatin-based treatment, followed by reintroduction on progression of disease [Adams *et al.* 2011]. Intermittent chemotherapy was associated with improved quality of life, reduced time on chemotherapy, and

fewer visits to the hospital. The small difference in OS in favor of continuous therapy should be weighed against the significantly reduced toxicity associated with intermittent treatment.

An important methodology limitation of these two studies (OPTIMOX2, COIN) was the randomization of patients before induction therapy, including patients in the intermittent arm who were not eligible for this strategy. Patients with progressive disease on induction therapy or amenable to salvage surgery biased the results. We now believe that decisions about chemotherapy holidays cannot be made before starting therapy. Despite these results, a significant number of patients can benefit from chemotherapy discontinuation. New criteria for chemotherapy discontinuation were defined from the findings for patients in the OPTIMOX1 and OPTIMOX2 studies who had a successful CFI and prolonged survival: a normal CEA level after 3 months of chemotherapy and chemotherapy

lasting 6 months before CFI [Perez-Staub *et al.* 2008]. In the COIN trial, patients with normal platelet counts at baseline were found to significantly benefit from a CFI [Adams *et al.* 2011].

Reintroduction and the concept of residual sensitivity

In the investigational arm of the OPTIMOX1 study, oxaliplatin was reintroduced in only 40% of patients and achieved a disease control rate of 69%. Despite the fact that a large number of patients did not receive the planned oxaliplatin reintroduction or received oxaliplatin after second-line therapy, both oxaliplatin reintroduction and the percentage of patients with oxaliplatin reintroduction per center had an independent and significant impact on OS [de Gramont *et al.* 2007]. Centers in which oxaliplatin was reintroduced in more than 40% of patients had an adjusted HR for OS of 0.59 compared with centers in which oxaliplatin was not reintroduced in any patients.

Defining oxaliplatin sensitivity is important for the therapeutic strategy when oxaliplatin reintroduction is feasible. As with platinum compounds in ovarian cancer, a prolonged interval (>6 months) between two periods of FOLFOX therapy and efficacy of first-line FOLFOX both predicted the efficacy of oxaliplatin reintroduction. Thus, reintroduction of oxaliplatin should be considered in patients who have an initial benefit from FOLFOX and who can tolerate it [de Gramont *et al.* 2009].

Intermittent chemotherapy

In the GISCAD study, 337 patients with previously untreated MCRC were randomized to receive irinotecan-based chemotherapy, either continuously until progression or intermittently (2 months on treatment, 2 months off) [Labianca *et al.* 2011]. There were no differences in PFS (HR = 0.88) or OS (HR = 1.03).

Endpoints in strategy trials

The increasing number of active compounds available for MCRC therapy dictates the strategy of trials evaluating these treatments either in combination or sequentially.

Overall survival

OS is the final accepted 'true' clinical outcome in cancer trials. OS is simple to measure and

measured without bias. However, OS has several drawbacks. First, death occurs after a relatively long time for most patients. Second, clinical trials using OS as the primary endpoint require a large number of patients and several years of follow up to demonstrate a statistically significant difference between the new treatment and the standard treatment, increasing the cost and duration of these trials. Finally, the effects of a drug on OS are diluted by the effects of crossover and subsequent therapies. Of note, OS represents the overall effect of several treatment lines. Therefore, OS may not be a sensitive endpoint to evaluate the effect of a new first-line therapy, or a new therapeutic strategy.

Alternative endpoints

Alternative outcomes that can be measured earlier are needed to shorten the duration and reduce the size and cost of clinical trials.

PFS evaluates the time to first progression or death from any cause if disease progression did not occur. This definition limits PFS to the direct measure of a single sequence of treatment until the occurrence of the first event. PFS is unconfounded by crossover but cannot evaluate a treatment strategy beyond first progression. In MCRC it has been shown that the treatment effects on OS, based on the effects on PFS, are predicted extremely well when patients receive no effective second-line therapy [Buyse *et al.* 2007]. However, the prediction may not be as good when patients receive subsequent active lines of treatment. Indeed, the benefit in PFS will be lost in OS when the median survival post progression (SSP) is large. This is particularly the case for MCRC because subsequent therapies are available after the first sequence of therapy (reintroduction, second- and third-line therapy).

Thus, considering that PFS and OS are not reliable endpoints to evaluate therapeutic strategies, new composite endpoints have been proposed to evaluate a chemotherapy strategy in MCRC: DDC, time to failure of strategy (TFS), and strategy failure-free survival (SFFS). DDC may be seen as a direct measure of the treatment effect of a therapeutic strategy by excluding uncontrolled disease intervals (time from disease progression to reinitiation of chemotherapy) and an inactive second course of treatment, defined as documented disease progression at the first tumor evaluation after reinitiation of full therapy. TFS, however, aims to evaluate a global treatment strategy. DDC and TFS were found to be strongly correlated with

OS [Chibaudel *et al.* 2011a]. SFFS, which looks like TFS, was recently evaluated in the MRC COIN trial. In the intermittent treatment group, a SFFS event occurred when a patient had progressive disease during a planned treatment period or within 8 weeks of starting a chemotherapy-free interval. In the continuous treatment group, SFFS was similar to PFS [Adams *et al.* 2011]. Contrary to PFS, these endpoints enable the duration of the therapeutic effect to be assessed before and after the first disease progression.

Ongoing strategy trials

These are summarized in Table 2.

Optimal timing for the use of anti-angiogenic and anti-epidermal growth factor agents

An important practical question for the majority of patients who have an unresectable tumor, even in the case of tumor shrinkage, is when to use anti-angiogenic agents and anti-EGF agents.

Three ongoing first-line phase III trials (CALBG 80405, FIRE-3, ML25686) are performing a comparison of a standard chemotherapy regimen in combination with either bevacizumab or cetuximab [Venook and Blanke, 2011; Heinemann, 2011; Hoffman-La Roche, 2011a]. Primary endpoints are OS in the CALGB trial, RR in the FIRE-3 trial, and PFS in the ML25686 trial. Of note, subsequent lines of treatment are not part of the trials.

The multiline GISCAD trial (second and third lines) is comparing two different treatment sequences (FOLFOX4 followed, after progression, by irinotecan/cetuximab or the reverse sequence) after failure of FOLFIRI/bevacizumab first-line therapy [Labianca, 2011]. The primary endpoint is OS.

Maintenance or chemotherapy-free interval?

Three trials are comparing bevacizumab-based maintenance therapy, either alone (AIO-KRK-0207, SWS-SAKK-41/06) or in combination with fluoropyrimidine (AIO-KRK-0207, CAIRO-3) to completely stopping therapy. In the AIO trial, patients are randomly allocated to one of three arms: bevacizumab with fluoropyrimidine (arm 1), bevacizumab alone (arm 2), or observation (arm 3) after 6 months of induction therapy with oxaliplatin-based chemotherapy

with bevacizumab [Hegewisch-Becker, 2011]. The primary endpoint is time to failure of maintenance and a reintroduction treatment strategy. In SWS-SaKK-41/06, patients are randomized after first-line therapy to maintenance with bevacizumab or completely stopping antitumor therapy [Koeberle, 2011]. The primary endpoint is time to progression. In the CAIRO-3 study, patients are randomly assigned to bevacizumab plus capecitabine or observation after 4.5 months of induction therapy with oxaliplatin, capecitabine, and bevacizumab [Punt, 2011]. The primary endpoint is PFS after reintroduction of chemotherapy and bevacizumab.

Maintenance: interest in double pathway inhibition?

Ongoing studies are further evaluating the role of targeted therapies alone during CFI. Both DREAM and ACT-2 studies are comparing maintenance therapy with bevacizumab alone or in combination with erlotinib. In the GERCOR-DREAM trial, patients are randomized after 3–6 months of induction chemotherapy (oxaliplatin based or irinotecan based) with bevacizumab, only in the case of controlled disease or when metastasis resection is not appropriate, whatever the KRAS mutation status [Tournigand, 2011]. In the ACT-2 study, the comparison is restricted to patients with wild-type KRAS tumors. The activity of bevacizumab and low-dose metronomic capecitabine is being explored in a third arm in patients with KRAS-mutated tumors [Johnsson, 2011].

Anti-angiogenic agent beyond progression

Should VEGF inhibition be carried over from first- to second-line therapy, meaning beyond progression? This question will be answered by the European ML18147 and the Italian GONO trials, which are investigating the use of bevacizumab beyond progression added to a sequential chemotherapy backbone in advanced colorectal cancer [Hoffman-La Roche, 2011b; Falcone, 2011]. The results of the ML18147 study should be available by the end of 2012.

Conclusions

The management of MCRC is a global treatment strategy, which applies several lines of therapy, salvage surgery, maintenance, and treatment-free intervals. Our knowledge is based on clinical trials performed in selected populations, of younger age, and with fewer comorbidities than the

Table 2. Ongoing phase III strategy trials in metastatic colorectal cancer.

NCT No.	Study name	Sponsor	N	Control arm	Investigational	Reference
<i>Bev versus CTX first line</i>						
00265850	C80405	CALGB	760	Chemo+bev	Chemo+CTX	(Venook & Blanke, 2011)
00433927	FIRE-3	LM-UM	568	FOLFIRI+bev	FOLFIRI+CTX	(Heinemann, 2011)
01338558	ML25686	Roche	825	mFOLFOX6+CTX	mFOLFOX6+bev	(Hoffman-La Roche, 2011a)
<i>CTX second or third line</i>						
01030042	COMETS	GISCAD	350	L2: FOLFOX4 L3: irinotecan+CTX	L2: irinotecan+CTX L3: FOLFOX4	(Labianca, 2011)
<i>Maintenance and/or observation</i>						
00544700	SWS-SAKK-41/06	SGCCR	238	Bev	Therapy-free interval	(Koeberle, 2011)
00442637	CAIRO3	DCCG	635	Cap+bev	Therapy-free interval	(Punt, 2011)
00973609	AIO-KRK-0207	AIO	760	Fluoropyrimidine+bev	Therapy-free interval or bev monotherapy	(Hegewish-Becker, 2011)
00265824	DREAM	GERCOR	700	Bev	Bev+erlotinib	(Tournigand, 2011)
01229813	ACT-2	LUH	181	Bev	WT-KRAS: Bev+erlotinib Mut-KRAS: Cap-Bev	(Johnsson, 2011)
<i>Bev beyond progression</i>						
00700102	ML18147	Roche	822	Chemo (no bev)	Chemo+bev	(Hoffman-La Roche, 2011b)
00720512	GONO-BEBYP-ASL607LIOM03	GONO	262	Chemo (no bev)	Chemo+bev	(Falcone, 2011)
AIO, Arbeitsgemeinschaft Internistische Onkologie (Germany); Bev, bevacizumab; CALGB, Cancer and Leukemia Group (US); CTX, cetuximab; DCCG, Dutch Colorectal Cancer Group (Netherlands); FOLFIRI, 5-fluorouracil/leucovorin/irinotecan regimen; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin regimen; GERCOR, Groupe Coopérateur Multidisciplinaire en Oncologie (France); GISCAD, Gruppo Italiano per lo studio dei Carcinomi dell'Apparato Digerente (Italy); GONO, Gruppo Oncologico del Nord-Ovest (Italy); LM-UM, Ludwig-Maximilians – University of Munich (Germany); LUH, Lund University Hospital (Sweden); Mut, mutant; N, estimated enrollment; NCT No., ClinicalTrials.gov Identifier; SGCCR, Swiss Group for Clinical Cancer Research (Swiss); WT, wild-type. Study acronyms are used for brevity: readers may refer to the cited references for full details of study names and details.						

general MCRC population. Thus, formal conclusions should be formulated carefully.

The treatment options available in clinical practice for patients with initially unresectable wild-type KRAS MCRC are shown in Figure 2. Randomized strategy trials (i.e. beyond first line) comparing these different options are needed to formally recommend the best strategy.

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