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Systemic Treatment in Recurrent and Metastatic Unresectable Rectal Cancer

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1. Introduction

Most patients with recurrent and metastatic rectal cancer cannot be cured. Selected patients with local recurrence or liver and/or lung-limited metastatic disease are sometimes curable with radiation therapy (RT) or surgery. However, for the majority of patients, treatment is palliative and systemic therapy remains the mainstay treatment. Over the last ten years, survival of patients with unresectable metastatic or recurrent rectal cancer has considerably improved. The median survival is about two years due to availability of new chemotherapy regimens and targeted therapies. For decades, 5-fluorouracil (5-FU) was the only active and available agent. Since the year 2000, irinotecan and oxaliplatin were approved. Access to all these three active agents strongly correlates with improved survival. More progress was achieved recently with the development of targeted therapies. Bevacizumab is a monoclonal antibody targeting the vascular endothelial growth factor (VEGF). Cetuximab and panitumumab are two monoclonal antibodies targeting the epidermal growth factor receptor (EGFR). Combinations of these different drugs are now commonly used.
In non-curable patients, goals are improvement of survival and quality of life. The purpose of this chapter is to review data from clinical trials evaluating systemic therapy in unresectable recurrent or metastatic rectal cancer. Commonly used chemotherapy regimens and biologic agents will be described as well as their side effects. General principles of treatment and specific treatment recommendations will also be discussed.

2. Chemotherapy

2.1 Fluoropyrimidines

Fluoropyrimidines have been used for the treatment of metastatic colorectal cancer (mCRC) for many years. 5-FU is a fluoropyrimidine that causes inhibition of thymidylate synthase and leads to impaired DNA synthesis. Adding folinic acid (leucovorin) intensifies the cytotoxic power of 5-FU stabilizing its bind to the enzyme. Different schedules of administration have shown clinical activity in different trials. Short-term infusional schedules have gained acceptance. A French study, compared a regimen of bolus 5-FU/LV day 1 to 5 every four weeks to bimonthly 5-FU/LV bolus over two hours followed by a 22 hours 5-FU infusion for two consecutive days. The infusional regimen showed better response rate (RR) and progression free survival (PFS). It was also associated with less

hematological and gastrointestinal (GI) toxicity. This "de Gramont regimen" is now a standard (de Gramont et al. 1997).

The widely used oral form of fluoropyrimidine is capecitabine. It is a prodrug that needs to be metabolized to 5-FU by multiple sequential enzymatic reactions. In 2001, a phase 3 randomized trial showed that use of oral capecitabine in first-line mCRC patients was more active than 5-FU/LV in the induction of objective tumor responses. Time to disease progression and survival were at least equivalent for capecitabine compared with the 5-FU/LV arm. Capecitabine also demonstrated clinically meaningful benefits over bolus 5-FU/LV in terms of tolerability although hand-foot syndrome was more common (Hoff et al. 2001). Similar results were observed in another identically designed randomized study (Van Cutsem et al. 2001).

Dihydropyrimidine dehydrogenase (DPD) is an important enzyme in the metabolism of fluoropyrimidines. It is the rate limiting enzyme in 5-FU catabolism. Patients who are deficient in DPD activity may have severe, even fatal toxicities such as severe diarrhea, mucositis and pancytopenia. For these patients, an alternative to 5-FU is raltitrexed which is a pure thymidylate synthase inhibitor. In a 2002 randomized study, raltitrexed showed similar RR and overall survival (OS) to the de Gramont regimen and was easier to administer, but resulted in greater toxicity (GI and hematological) and inferior quality of life (Maughan et al. 2002).

Fluoropyrimidines alone had been the standard first-line treatment of mCRC until the development of combination regimens with irinotecan or oxaliplatin. Fluoropyrimidine monotherapy remains a valid option for patients with contraindications to combined therapies. The infusional regimen (de Gramont) is the preferred fluoropyrimidine monotherapy. Capecitabine is a safe oral alternative to 5-FU.

2.2 Irinotecan (table 1)

Irinotecan is a topoisomerase I inhibitor and has demonstrated efficacy in mCRC as a single agent or in association with a fluoropyrimidine. Irinotecan in monotherapy showed superiority to best supportive care alone after 5-FU failure. A randomized trial showed that the OS was significantly better in the irinotecan group ($p=0.0001$), with 36.2% 1-year survival in the irinotecan group versus 13.8% in the supportive-care group. Quality of life was also better with less tumor related symptoms. In this trial, irinotecan was given every three weeks (Cunningham et al. 1998).

A randomized trial showed an advantage in RR, time to progression (TTP) and median survival for combined treatment with irinotecan/5-FU/LV over 5-FU/LV alone in first-line mCRC. An infusional regimen was used (the Douillard regimen). Treatment was given weekly or every two weeks. There were more toxicities in the irinotecan arm (diarrhea and neutropenia) but they were manageable (Douillard et al. 2000). Results of the BICC-C study suggest that the infusional regimen (FOLFIRI) is associated with better PFS and less toxicities compared to the bolus regimen (IFL).

The use of oral capecitabine associated with irinotecan (CapeIRI) was also assessed in the BICC-C study. It was compared to FOLFIRI and IFL. It was associated with more toxicities and less efficacy (Fuchs et al. 2007).

Late diarrhea and neutropenia are the main dose-limiting toxicities from irinotecan. UGT1A1 polymorphism predicts irinotecan toxicity. Irinotecan can also cause early-onset symptoms of cholinergic excess including diarrhea, abdominal cramping, lacrimation, rhinitis and salivation.

Regimen	Irinotecan	Leucovorin	5-FU*/capecitabine	Schedule
FOLFIRI *Fuchs et al. 2007*	180 mg/m² IV over 90 min day 1	400 mg/m² IV over 2 h day 1	*400 mg/m² IV bolus day 1; 2400 mg/m2 IV continuous infusion over 46 h	Every two weeks
IFL *Saltz et al.2000*	125 mg/m² IV bolus	20 mg/m² IV bolus	*500 mg/m² IV bolus	Weekly for four weeks every six weeks
mIFL *Fuchs et al. 2007*	125 mg/m² IV over 90 min on days 1 and 8	20 mg/m² IV bolus on days 1 and 8	*500 mg/m² IV bolus on days 1 and 8	Every three weeks
CapeIRI *Fuchs et al. 2007*	250 mg/m² IV over 90 minutes day 1		Capecitabine by mouth 1000mg/m² twice a day on days 1 to 14	Every three weeks

Table 1. Irinotecan Regimens

2.3 Oxaliplatin (table2)

In 1998, the platinum derivative, oxaliplatin when given together with 5-FU was shown to have significant activity in mCRC (deBraud et al. 1998). The activity of oxaliplatin alone in mCRC is low (Rothenberg et al. 2003). In 2000, a study showed better PFS and RR with the addition of oxaliplatin to 5-FU/LV compared to 5-FU/LV infusional regimen alone as first-line treatment in advanced colorectal cancer (de Gramont et al. 2000).

The combination of oxaliplatin and oral capecitabine (XELOX or CAPOX) has also been studied and compared to other fluoropyrimidine/oxaliplatin combinations in multiple randomized studies. A pooled analysis of randomized trials comparing first-line CAPOX to oxaliplatin in combination to infusional 5-FU/LV showed that CAPOX resulted in lower RR, but this did not affect PFS and OS. The toxicity analysis showed thrombocytopenia and hand-foot syndrome were consistently more prominent with the CAPOX regimens (Arkenau et al. 2008). CAPOX may be considered in patients where ambulatory infusion is not possible or refused.

In 2004, Tournigand and colleagues randomly assigned previously untreated patients to FOLFOX 6 or FOLFIRI. At progression, irinotecan was replaced by oxaliplatin or oxaliplatin by irinotecan. Both strategies showed equivalent RR (about 55%) and median survival (20.6 and 21.5 months). Nausea, mucositis and alopecia were more common with FOLFIRI while neutropenia and paresthesias were more common with FOLFOX (Tournigand et al. 2004). An Italian study showed similar findings (Colucci et al. 2005).

Thus, using FOLFOX or FOLFIRI in first-line treatment and then switching to the alternate regimen at progression or treatment intolerance is widely accepted. The decision of choosing one regimen over the other will be influenced by toxicity profile and patient preference.

One of the main concerns with the use of oxaliplatin is neurotoxicity. Acute neurotoxicity and cumulative sensory neuropathy are described. The acute neurotoxicity typical symptoms are dysesthesias of hands, feet and perioral region. More rarely, pharyngeal dysesthesias can be observed. These symptoms are generally triggered by cold, are associated with higher doses of oxaliplatin and are infusion-rate dependant. In 2008, Petrioli and colleagues suggested a prolonged infusion time to reduce the acute toxicity (Petrioli et al. 2008). This acute toxicity seems to be related to hyperexcitability of the peripheral nerves which has been attributed to disruption in cell membrane ion channels (Wilson et al. 2002; Park et al. 2009). In contrast, the cumulative neuropathy is generally sensory, symmetrical and without motor involvement. Oxaliplatin-induced cumulative sensory neuropathy occurs after several cycles of therapy (Cassidy et al. 2002). In about three fourths of patients, neurotoxicity is reversible with a median time to recovery of 13 weeks after treatment discontinuation. Strategies have been developed to prevent oxaliplatin-induced cumulative neurotoxicity. First, new schedules of administration were investigated. The Optimox-1 study randomly assigned patients to FOLFOX 4 (oxaliplatin 85 mg/m2) until progression or to six cycles of FOLFOX 7 (oxaliplatin 130mg/m2) followed by maintenance 5FU-LV for 12 cycles. FOLFOX 7 was then reintroduced for non progressive patients. RR, PFS and survival were similar in both arms. Grade 3 and 4 neuropathy was reduced in FOLFOX 7 arm after the sixth cycle even though it occurred earlier. The conclusion was that oxaliplatin can be safely stopped after six cycles in a FOLFOX 7 regimen (Tournigand et al. 2006). The Optimox-2 study compared a chemotherapy-free interval with maintenance 5-FU/LV after six cycles of modified FOLFOX 7 (mFOLFOX7) chemotherapy in the first-line treatment of mCRC. mFOLFOX 7 was reintroduced for patients with progressive disease in both arms. Duration of disease control (DDC) and PFS were better in the maintenance arm (Chibaudel et al. 2009). Thus oxaliplatin-free intervals are feasible but complete discontinuation of chemotherapy may be associated with inferior outcomes. Secondly, the benefit of use of IV calcium (Ca) and magnesium (Mg) in order to diminish neuropathy symptoms was suggested in randomized trials. In 2011, Grothey and colleagues showed that IV Ca/Mg is an effective neuroprotectant against oxaliplatin-induced cumulative neuropathy in adjuvant colon cancer. The incidence of grade 2 or greater cumulative sensory neurotoxicity was significantly reduced. The onset of grade 2 or greater sensory neurotoxicity was also delayed in patients receiving Ca/Mg (Grothey et al. 2011). This study had a low statistical power due to early closure of the trial because preliminary reports from another trial (CONcePT trial) that initially suggested decreased response rates for patients getting Ca/Mg (Hochster et al. 2007). This was later proven untrue by an independent radiologic review.

2.4 Other chemotherapy combinations (table 2)

The combination of oxaliplatin and irinotecan (IROX) has been assessed in first and second line setting. In the first-line setting, IROX was shown to be inferior and more toxic in elderly patients compared to FOLFOX (Sanoff et al. 2008) and equivalent to FOLFIRI (Fischer von Weikersthal et al.2011). In the second-line setting, IROX was compared to a triple regimen of 5FU/LV with alternating irinotecan and oxaliplatin. RR (23 versus 6 percent) and median survival (12.3 versus 9.8 months) were better with IROX but the doses of irinotecan and oxaliplatin were smaller in the triple therapy arm (Bécouarn et al. 2001). The efficacy of FOLFOXIRI regimen has been evaluated in two randomized studies. An Italian study

showed better RR (41 versus 66 percent), PFS (9.8 versus 6.9 months) and OS (22.6 versus 16.7 months) for FOLFOXIRI compared to FOLFIRI in the first-line setting. This was in a selected population of patients in good general condition and with favorable features. More toxicities were reported in the FOLFOXIRI arm especially in terms of neutropenia and neurotoxicity (Falcone et al.2007). This benefit and its cost in terms of toxicities were confirmed in a systematic review (Montagnani et al. 2010). In contrast, a Greek phase 3 randomized failed to show benefits to FOLFOXIRI when compared to FOLFIRI (Souglakos et al. 2006). However, compared to the Italian trial, lower doses of oxaliplatin, irinotecan and 5-FU were used.

Regimen	**Oxaliplatin**	**Irinotecan**	**Leucovorin**	**5-FU/cape**	**Schedule**
CAPOX *Hochster et al. 2008*	130mg/m² IV on day 1			capecitabine 1,000 mg/m² orally twice daily on days 1 to 15	Every three weeks
IROX *Goldberg et al. 2004*	85mg/m²	200 mg/m²			Every three weeks
FOLFOX 4 *Goldberg et al. 2004*	85 mg/m² on day 1		200 mg/m² day 1	bolus FU 400 mg/m² followed by FU 600 mg/m² in 22-hour infusions on days 1 and 2	Every two weeks
FOLFOX 6 *Tournigand et al. 2004*	100 mg/m² day 1		400 mg/m² day 1	bolus FU 400mg/m² followed by infusion 2400-3000 mg/m² over 46 hours	Every two weeks
FOLFOX 6 modified *Hochster et al. 2008*	85 mg/m² day 1		400 mg/m² day 1	bolus FU 400mg/m² followed by infusion 2400 mg/m² over 46 hours	Every two weeks
bFOL *Hochster et al. 2008*	85 mg/m² on days 1 and 15		20 mg/m² days 1, 8 and 15	500 mg/m² push days 1,8 and 15	Every four weeks
FOLFOX 7 *Tournigand et al. 2006*	130 mg/m² day 1		400 mg/m² day 1	infusion 2400 mg/m² over 46 hours	Every two weeks
FOLFOX 7 modified *Chibaudel et al. 2009*	100 mg/m² day 1		400 mg/m² day 1	infusion 3000 mg/m² over 46 hours	Every two weeks
FOLFOXIRI *Falcone et al. 2007*	85 mg/m² day 1	165 mg/m² day 1	200 mg/m² day 1	Infusion 3200 mg/m² over 48h	Every two weeks

Table 2. Oxaliplatin Regimens

3. Targeted therapies

Targeted cancer therapies are drugs that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. Bevacizumab, cetuximab and panitumumab are three monoclonal antibodies which have known efficacy in mCRC.

3.1 Angiogenesis inhibitors

3.1.1 Bevacizumab

Bevacizumab is a monoclonal humanized antibody targeting the VEGF. It is assumed that bevacizumab normalizes the vascular environment and improves the chemotherapy delivery to the tumor.

Bolus IFL (irinotecan/5-FU/LV) plus bevacizumab (5mg/kg) was compared to IFL plus placebo in previously untreated patients with mCRC. They observed statistically better RR, PFS and OS (20.3 versus 15.6 months). This was the pivotal study which led to the approval of bevacizumab in the treatment of mCRC. Grade 3-4 high blood pressure (HBP) was significantly increased in the bevacizumab arm (Hurwitz et al. 2004). FOLFIRI regimen has however gained acceptance over the bolus IFL regimen due to a more favorable toxicity profile. The BICC-C trial showed a significant advantage in terms of median survival with FOLFIRI plus bevacizumab compared to mIFL plus bevacizumab (28 versus 19 months, p=0.037) (Fuchs et al. 2007). Several trials have also addressed the benefit of adding bevacizumab to an oxaliplatin-based regimen. In a phase 2 cohort study (TREE-2), three oxaliplatin-containing regimens (FOLFOX, bolus 5FU and oxaliplatin-bFOL, CAPOX) were investigated in association with bevacizumab. Median survivals were respectively 26.1, 20.4 and 24.6 months (Hochster et al. 2008). Median OS was 23.7 months for the combined group treated with bevacizumab compared to 18.2 months for patients who did not received bevacizumab.The benefit of adding bevacizumab to oxaliplatin-containing chemotherapy appeared however to be more modest in the NO16966 trial. The addition of bevacizumab to FOLFOX4 or XELOX resulted in an increase of PFS of 1.4 months but the superiority of bevacizumab was statistically evident only in the XELOX subgroup (p=0.0026). Additionally, the OS significance did not reach statistical difference (21.3 months vs. 19.9 months) and the RR was similar in both groups (47% vs. 49%) (Saltz et al. 2008). The use of bevacizumab in first line is nevertheless widely accepted with either FOLFOX or FOLFIRI. In a phase 2 randomized study 5-FU/LV plus placebo was compared to 5-FU/LV plus bevacizumab. The bevacizumab-based treatment showed significant better PFS and non significant better OS (Kabbinavar et al. 2005). Thus, 5-FU/LV plus bevacizumab remains an option for patients with contraindications to other regimens.

The addition of bevacizumab in second-line treatment was assessed in the ECOG 3200 trial. Patients previously treated with a fluoropyrimidine and irinotecan were randomly assigned to receive FOLFOX4 in combination with bevacizumab (at 10 mg/kg), FOLFOX4 or bevacizumab alone. This study showed better PFS and OS in the FOLFOX4 plus bevacizumab arm. No activity was shown with bevacizumab alone (Giantonio et al. 2007). In contrast, there is no strong enough evidence to continue bevacizumab beyond progression in first-line treatment although favorable data is suggested by the BRITE study. This cohort study showed encouraging survival rates in patients who received post-progression chemotherapy with continued bevacizumab (Grothey et al. 2008).

Bevacizumab is associated with several toxicities such as proteinuria, bleeding, HBP, arterial thromboembolic events (ATE) and gastrointestinal perforations (Kabbinavar et al. 2005). Thus high risk patients with comorbidities such as elderly patients and patients with historic of ATE or bleeding should be identified and carefully monitored if bevacizumab is administered. Also, because VEGF is involved in wound healing, bevacizumab should be stopped at least five weeks before any surgery.

3.2 Anti-EGFR monoclonal antibodies

Cetuximab and panitumumab are monoclonal antibodies targeting the extracellular domain of the EGFR (epidermal growth factor receptor). *KRAS* mutations cause permanent activation of the downstream cascade and result in failure to respond to anti-EGFR monoclonal antibodies (Bardelli et al. 2010) (figure 1). *KRAS* mutations are detected in approximately 40% of mCRC. These mutations are mainly found in codons 12 and 13. Recent studies suggest however that not all mutations confer the same resistance to anti-EGFR therapy. Nevertheless, *KRAS* mutation is a predictive biomarker for anti-EGFR therapy and tumor *KRAS* status should be determined whenever anti-EGFR therapy is considered in the treatment of mCRC. According to ASCO's provisional clinical opinion, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations in an accredited laboratory. If *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment (Allegra et al. 2009).

Other mutations probably confer resistance to anti-EGFR therapy. *BRAF* mutation is found in 5 to 10 % of colorectal cancer tumors. *KRAS* and *BRAF* mutations are mutually exclusive. The *BRAF* mutation has been recognized as a negative prognostic marker but recent data does not confirm it as a negative predictive marker for anti-EGFR therapy. *PIK3CA* mutations/*PTEN* expression, amphiregulin and epiregulin are other potential predictive biomarkers but further supportive, preferably prospective, studies confirming their role as predictive biomarkers for anti-EGFR therapy would be necessary before considering their use in routine clinical practice in this regard.

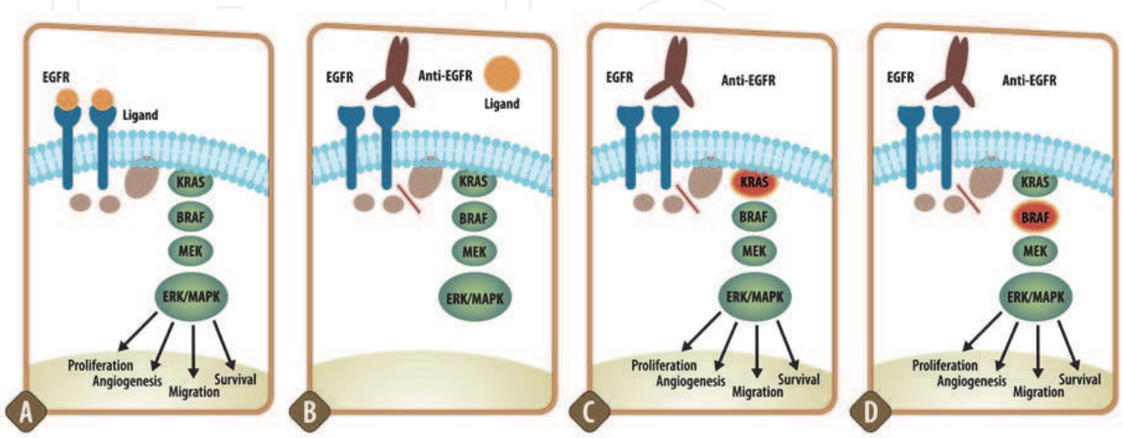

Fig. 1. EGFR Signal Transduction

Cetuximab is associated with severe infusion reaction in three percent of patients. Ninety percent occur during the first infusion and generally in the three first hours. Premedication with anti H1 antagonist and/or glucocorticoid is recommended (Wilke et al. 2008). Panitumumab is generally associated with less infusion reaction because of its 100% human origin. Cetuximab and panitumumab may be also associated with a magnesium-wasting syndrome. Serum levels of this electrolyte should be carefully monitored during treatment. Acneiform eruption occurs in two third of patients treated anti-EGFR molecules. Some studies suggest benefit from using prophylactic antibiotics such as minocyline or doxycycline and topical application of hydrocortisone-based cream (Scope et al. 2007; Lacouture et al. 2010).

3.2.1 Cetuximab (table 3)

Cetuximab is a chimeric (mouse/human) monoclonal antibody against the EGFR. In mCRC, cetuximab has shown efficacy in monotherapy as well as in combination with chemotherapy. It can be used in previously mCRC treated patients or in first-line therapy.

In 2007, cetuximab alone was compared to best supportive care (BSC) in the CO-17 trial. Patients had immunohistochemically detectable EGFR, previously been treated with fluoropyrymidines, irinotecan and oxaliplatin or had contraindications to treatment with these drugs. Survival was significantly better in the cetuximab arm (6.1 vs. 4.6 months). Quality of life was better preserved in the cetuximab group. Cetuximab was associated with a skin rash; grade 2 or higher grade rashes were strongly associated with improved survival (Jonker et al. 2007). In a subsequent analysis, in patients with mutated *KRAS* tumors, there was no significant difference between those who were treated with cetuximab and those who were treated with best supportive care. For wild-type (wt) *KRAS* patients, PFS (3.7 versus 1.9 months) and median OS (9.5 versus 4.8 months) were significantly improved by treatment with cetuximab as compared with best supportive care alone (Karapetis et al. 2008).

In the BOND study, a randomized phase 2 trial, irinotecan plus cetuximab was compared to cetuximab alone for patients refractory to irinotecan. RR and TTP were significantly better in the irinotecan plus cetuximab arm (22.9% vs. 10.8% and 4.1 vs. 1.5 months). There was a trend for better survival also in this arm as well (Cunningham et al. 2004).

In the EPIC trial, adding cetuximab to irinotecan after first-line fluoropyrimidine and oxaliplatin treatment failure, improved RR (16.4 percent versus 4.2 percent), PFS (4.0 versus 2.6 months) and quality of life compared with irinotecan alone (Sobrero et al. 2008; table 3).

Trials have also evaluated the efficacy of cetuximab in combination with chemotherapy in first-line treatment of mCRC. In the phase III CRYSTAL trial, the efficacy of cetuximab plus irinotecan, fluorouracil, and leucovorin (FOLFIRI) was investigated as first-line treatment for metastatic colorectal cancer. There was a significant advantage in RR, PFS and OS for the cetuximab group, but this benefit was limited to *KRAS*-wt patients (Van Cutsem et al. 2010).

In the randomized phase II multicenter OPUS trial, the addition of cetuximab to FOLFOX4 was associated with improved outcomes compared to FOLFOX4 alone in first-line treatment. A statistically significant better chance of response and PFS was shown in patients with *KRAS* wild-type tumors (Bokemeyer et al. 2009; table 3). Patients with mutant

KRAS tumors did not benefit, and may actually have been harmed, with the addition of cetuximab (RR of 33% vs. 49% in the FOLFOX4 alone group (p=0.106)). The phase III COIN trial is another important study which has evaluated the effect of addition of cetuximab to first-line oxaliplatin-based regimens treatment for advanced colorectal cancer. The choice of fluoropyrimidine (either 5-FU or capecitabine) was decided by the treating physician prior randomization (66% of the patients received oxaliplatin plus capecitabine). In patients with wt-*KRAS* tumor, the addition of cetuximab to oxaliplatin- based chemotherapy was associated with a small increase in best overall response (64% vs. 57%, P=0.049). In contrast to CRYSTAL and OPUS studies, however, the addition of cetuximab was not associated with any significant improvement in OS or PFS. (Maughan et al. 2011). Discrepancy between these studies remains difficult to explain.

3.2.2 Panitumumab (table 3)

Panitumumab is a fully human monoclonal antibody targeting the extracellular domain of EGFR. Similarly to cetuximab, panitumumab has shown efficacy in previously mCRC treated patients as well as in first-line therapy.

In patients refractory to 5-FU, irinotecan and oxaliplatin, panitumumab monotherapy showed significantly improved PFS from 7.3 to 8 weeks (p<0.001) and RR (10 percent versus 0 percent) compared to BSC alone. There was no OS benefit, likely due to panitumumab use after crossover in the BSC alone. Skin toxicities, hypomagnesaemia, and diarrhea were the most common toxicities observed (Van Cutsem et al. 2007). In this study, the effect on PFS in the wt-*KRAS* group was significantly higher than in the mutant group. Median PFS in the wt-*KRAS* group was 12.3 for panitumumab versus 7.3 weeks for BSC. RR was 17 percent for wt-*KRAS* versus 0 percent for patients with mutant *KRAS* tumors. This showed that panitumumab monotherapy efficacy is confined to wt-*KRAS* tumors and that this status should be considered in selecting patients for panitumumab monotherapy (Amado et al. 2008). In 2010, the FOLFIRI/panitumumab combination was compared to FOLFIRI alone in second-line treatment. In the *KRAS*-wt patients, when panitumumab was added to FOLFIRI median PFS was 5.9 months versus 3.9 months for FOLFIRI alone (p=0.004)(Peeters et al. 2009).

Panitumumab, in conjunction with chemotherapy regimen, has also been evaluated in first-line therapy for mCRC. In 2010, Douillard and colleagues compared FOLFOX 4 and panitumumab versus FOLFOX 4 alone as first-line chemotherapy for previously untreated mCRC (PRIME study). In the *KRAS*-wt patients, panitumumab-FOLFOX4 combination significantly improved PFS compared with FOLFOX4 (median PFS, 9.6 v 8.0 months, respectively; p=0.02). In the *KRAS*-mutant patients, outcome was significantly worse with panitumumab underscoring the importance of *KRAS* screening (Douillard et al. 2010).

Several studies have assessed the use of a dual antibody modality. The PACCE study evaluated the addition of panitumumab to bevacizumab and chemotherapy (oxaliplatin- and irinotecan-based) as first-line treatment for mCRC (Hecht et al. 2009). This study was stopped due to an interim analysis showing inferior PFS and more toxicities in the panitumumab arm. The CAIRO 2 study assigned untreated metastatic colorectal cancer to capecitabine, oxaliplatin, and bevacizumab or the same regimen plus weekly cetuximab. PFS was worse in dual antibody therapy (Tol et al. 2009).These results suggest that dual antibody therapy should not be considered outside further clinical trials.

Trial	Agent	Line	Chemotherapy	Results (**KRAS*-wt patients)
CRYSTAL *Van Cutsem et al. 2011*	Cetuximab	First	FOLFIRI	Median PFS*: 9.9 vs. 8.4 months HR 0.696 (p=0.0012) Median OS*: 23.5 vs. 20.0 months HR 0.796 (p=0.0093)
OPUS *Bokemeyer et al. 2009*	Cetuximab	First	FOLFOX 4	Overall RR*: 61% vs. 37% (p=0.011) Median PFS*: 7.7 vs. 7.2 months (p=0.0163)
COIN *Maughan et al. 2011*	Cetuximab	First	Oxaliplatin with 5FU or capecitabine	ORR*: 64% vs. 57% (p=0.049) No significant improvement in OS or PFS with the addition of cetuximab
PRIME *Douillard et al. 2010*	Panitumumab	First	FOLFOX 4	Median PFS*: 9.6 vs. 8 months (p=0.02)
EPIC *Sobrero et al.2008*	Cetuximab	Second	Irinotecan	PFS: 4 vs. 2.6 months (p<0.0001) RR: 16.4% vs. 4.2% (p<0.0001) OS: 10.7 vs. 10.0 months (p=0.71) but 46.9% of the patients in the irinotecan group received cetuximab after trial. (*KRAS* unselected)
STUDY 181 *Peeters et al*. 2010	Panitumumab	Second	FOLFIRI	Median PFS*: 5.9 vs. 3.9 months (p=0.004)

Table 3. Randomized Trials of Anti-EGFR-chemotherapy Association

4. Local recurrence

The treatment of locally recurrent disease largely depends on prior treatments. Whether the patient had prior surgery and/or radiation will determine the therapeutic approach. Surgery alone may be an option if negative surgical margins can be achieved. Extensive surgery is generally required. Combined therapies including chemotherapy and radiation (if prior radiation was not administered) are favored. In this setting the addition of chemotherapy to radiation before surgery improved local control, time to treatment failure, and cancer-specific survival compared with RT alone in a Norwegian phase 3 randomized study (Braendengen et al. 2008). Still this data has to be considered carefully because the patients in this study had primary unresectable tumors as well as local recurrences and that prior radiation was not allowed. Patients with local recurrence were more likely to be unresectable after preoperative treatment. Trends to improved local control were seen in a retrospective study from the Mayo clinic with the addition of 5-FU to external beam radiotherapy, intraoperative electron beam and surgery (Gunderson et al. 1996).

5. Summary and recommendations

Striking advances have been made in the treatment of metastatic colorectal cancer in the past fifteen years. In 2004, Grothey and colleagues reviewed seven published phase III trials

in advanced CRC. Their conclusion was that the three active drugs in mCRC (5-FU/LV, irinotecan and oxaliplatin) should be available to all patients in order to maximize the OS (Grothey et al. 2004). For patients with good performance status, combination therapy (FOLFOX or FOLFIRI) should be preferred as first-line chemotherapy. The choice of regimen should be based on the different toxicity profile of these two regimens. Fragile patients are not candidates for combination therapy but can benefit from treatment with fluoropyrimidine monotherapy. Infusion regimens are associated with less toxicity and should be used in any regimen. The use of oral capecitabine in regimens such as CAPOX is also a valid option for patients for whom infusion is not possible or refused. Different strategies can be used in an attempt to prevent oxaliplatin-induced neuropathy. It remains unclear if a combination regimen such as FOLFOXIRI is superior to FOLFOX or FOLFIRI combined with bevacizumab or an anti-EGFR monoclonal antibody. FOLFOXIRI is associated with significant toxicity and its use is not yet standard in first-line treatment of mCRC. The addition of bevacizumab, a monoclonal antibody targeting the VEGF, is now widely recommended with FOLFIRI, FOLFOX or fluoropyrimidine monotherapy in first-line therapy of mCRC for patients without contraindications to this agent. The use of bevacizumab in second-line setting is also recommended in patients who did not receive this agent in first-line treatment. The benefit of its use beyond progression remains controversial and is not presently recommended. Bevacizumab is associated with potentially serious toxicities so careful attention and monitoring of expected side effects is mandatory. Anti-EGFR monoclonal antibodies, cetuximab and panitumumab, are associated with improved outcomes when used as single agents as salvage therapy in patients with chemotherapy-refractory mCRC and when used for first-line and second-line therapy of mCRC in conjunction with chemotherapy regimens. However, their benefit is restrained to patients whose tumor does not harbour *KRAS* mutation. It is unknown whether adding EGFR inhibitors to initial therapy or using it in a sequential approach as a component of second or third –line therapy gives better results. Also, for now, it is not clear whether bevacizumab or anti-EGFR inhibitor should be preferentially added to first-line therapy. Indeed, chemotherapy plus bevacizumab currently represents the most widely accepted standard for first-line treatment of mCRC. Results from the current North American CALGB/SWOG cooperative group trial of best chemotherapy plus either bevacizumab or cetuximab in untreated *KRAS*-wt metastatic colorectal patients will help in guiding this decision. Although there are no trials directly comparing panitumumab to cetuximab, these agents appear to have comparable efficacy and they are probably interchangeable. Treatment must be individualized as always, taking into account goals of therapy, *KRAS* mutation status, and the toxicity profiles of each agent. Inclusion of patients in clinical trials should always be encouraged if possible.

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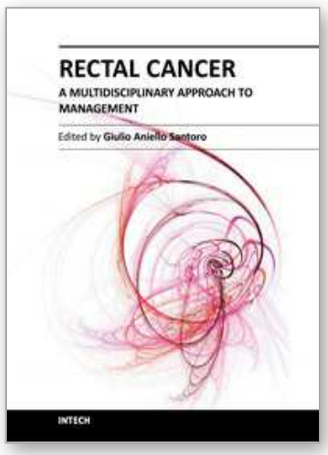

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Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

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