Improving outcomes in patients with metastatic colorectal cancer: progress in the quest for tailored, targeted therapy

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Introduction

The search for anticancer therapies that effectively attack malignant cells but do not cause the nonspecific toxicities associated with conventional chemotherapy has led to the development of agents that target the intracellular pathways known to be important in the development and progression of certain cancers. Targeted therapies are generally associated with better tolerability profiles than conventional agents, and advances in our understanding of molecular biology over recent decades have yielded an ever-increasing supply of potential targets.

It has become apparent, however, that there are many ways in which cancer cells can overcome or bypass cell cycle control mechanisms, and that the more finely targeted the agent, the more important it becomes to prospectively identify individuals whose cancer will be vulnerable to that particular agent. Thus, in this age of targeted agents, we are also increasingly entering the age of individualization of anticancer therapies. The race is on, not only to identify agents that will interfere with pathways known to be dysfunctional in particular types of cancers, but also to identify reliable, accessible, biological markers that are predictive of response to that agent. In the near future, anticancer medicine will be tailored to the individual patient, and to the individual cancer affecting the patient.

Colorectal cancer (CRC) is the second most common cause of cancer-related death in Europe.[1] Surgery remains the only curative approach to this disease, but only 15% of patients with metastatic CRC (mCRC) are eligible for a potentially curative surgical approach at presentation. Approximately 25% of patients with CRC present with overt metastatic disease, and 40–50% of newly diagnosed patients will eventually develop metastatic disease. Few patients with unresectable mCRC survive beyond 5 years.[2]

When CRC is considered to be beyond primary curative surgery, initial treatment may be applied with the intention to make a surgical approach possible, but thereafter treatment is used to slow disease progression. In patients who present with mCRC, treatment that improves resectability (i.e. neoadjuvant treatment) is the only known way to increase the chance of a cure. Otherwise, treatment is directed to control the disease for as long as possible while maintaining the patient's quality of life.

The immunoglobulin (Ig) G1 monoclonal antibody cetuximab (Erbitux®) targets the epidermal growth factor receptor (EGFR), blocking interaction with the natural ligand(s) and thus inhibiting growth signals initiated by receptor–ligand interaction. This pathway is important in the progression of CRC, and cetuximab has been approved for the treatment of EGFR-expressing mCRC in more than 65 countries, in the second-line and later settings. This agent has consistently been shown to improve overall response rate (ORR) and progression-free survival (PFS) when used in combination with chemotherapy in patients who have failed prior oxaliplatin-based or irinotecan-based chemotherapy.[3,4] Cetuximab has also been shown to improve survival as a single agent.[5]

In common with other cancer therapies, only a proportion of patients gain advantage from the addition of cetuximab to chemotherapy. Recent research on the intracellular pathway initiated by EGFR ligand binding has suggested a potential biomarker for responsiveness to this agent, KRAS (Kirsten RAt Sarcoma), the protein product of the KRAS proto-oncogene, which is frequently mutated in a variety of solid tumors.[6]

KRAS: a molecular switch in the EGFR pathway

KRAS protein is a member of the RAS family of small guanosine nucleotide-binding proteins, and is a downstream component of EGFR signaling, relaying growth-promoting signals from the cell surface to the nucleus. It can be regarded as a molecular switch and its physiological function is characterized by the change from an inactive guanosine diphosphate (GDP)-binding state to an active guanosine triphosphate (GTP)-binding state.[6,7] The EGFR, a receptor tyrosine kinase, autophosphorylates when ligand binding leads to dimerization, which in turn leads to the activation of KRAS, which passes on growth-promoting signals through complex intracellular signaling cascades, including the RAF-1-MEK-MAPK pathway (Figure 1). As part of the normal physiological signaling process, activated KRAS switches itself off through its intrinsic GTPase activity, which hydrolyzes bound GTP to GDP, returning the protein to its inactive conformation. The link between mutated KRAS and cancer has been demonstrated *in vitro*. Expression of mutated KRAS alleles from human tumors in cell line model

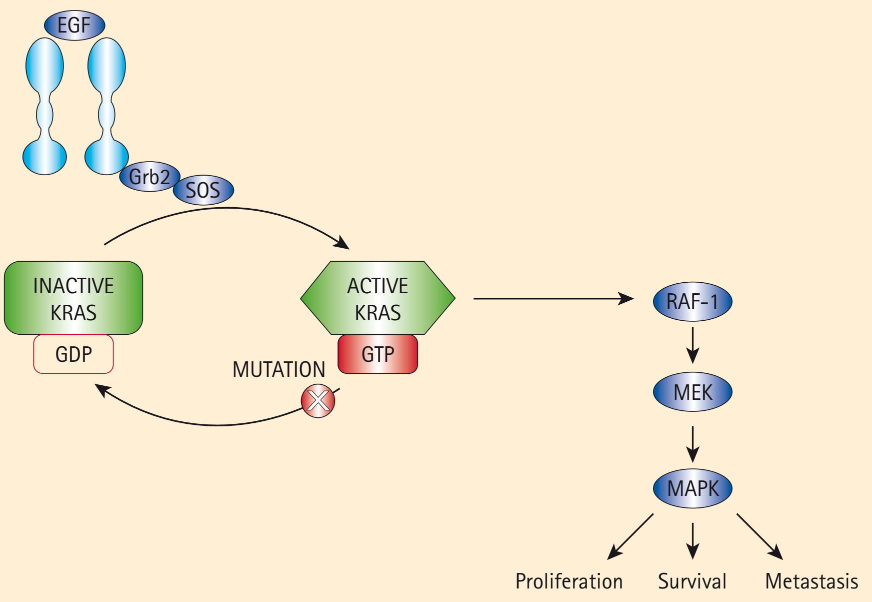

Figure 1
KRAS in epidermal growth factor receptor signaling and cancer.
EGF, epidermal growth factor; GDP, guanosine diphosphate; Grb2, Growth factor receptor-bound protein 2; GTP, guanosine triphosphate; KRAS, protein product of KRAS proto-oncogene; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; RAF-1, protein product of c-raf gene; SOS, GTPase 'Son of Sevenless'.

systems has been shown to cause malignant transformation of cell lines, and targeting KRAS has been shown to inhibit their growth.[8,9] The most frequent (~90%) site of KRAS mutation is in codons 12 and 13, which encode conserved residues of the guanine nucleotide-binding domain of the protein. These mutations lock KRAS in the active GTP-bound state by impairing the GTPase activity of the protein, thus eliminating the physiological mechanism that ensures only transient activation of KRAS.[10,11] Constitutive activation of KRAS leads to a loss of control of cell proliferation and survival, and the promotion of metastasis.

KRAS mutation status: a potential biomarker for responsiveness to anti-EGFR agents

Mutations conferring constitutive activation of KRAS are commonly found in a variety of solid tumors.[7] In theory, constitutive activation of KRAS should render anti-EGFR agents ineffective because the EGFR signaling cascade will be turned on whether or not EGFR dimerization and autophosphorylation occurs (Figure 1). Thus, KRAS mutation status could be a biomarker for responsiveness to agents such as cetuximab, which act upstream of KRAS in the EGFR signaling cascade.

Investigations in nonrandomized, single-arm clinical trials in patients with previously treated mCRC support the hypothesis that KRAS mutation status is a biomarker for responsiveness to EGFR-directed agents (Table 1).

In a retrospective study of 89 patients with mCRC who had received cetuximab as monotherapy or in combination with irinotecan or FOLFIRI (FOLinic acid/5-Fluorouracil /IRInotecan) after failure of irinotecan-based chemotherapy, Lièvre

Table 1
Influence of KRAS status on efficacy of cetuximab in metastatic colorectal cancer: retrospective analyses of single-arm studies.

Reference	N	KRAS wild type (%)	Influence of KRAS status	
			Effect	***p* value**
Lièvre *et al.* 2006[12]	30	57	Response rate higher in KRAS wild-type Median OS longer in KRAS wild-type	0.003 0.016
Lièvre *et al.* 2008[13]	89	73	Response rate higher in KRAS wild-type Median OS longer in KRAS wild-type	<0.01 0.026
Di Fiore *et al.* 2007[14]	59	63	Progressive disease associated with KRAS mutant tumors Time to progression longer in KRAS wild-type	0.005 0.015
Finnocchiaro *et al.* 2007[15]	85	62	Response rate higher in KRAS wild-type	0.02
Khambata-Ford *et al.* 2007[16]	80	62	Disease control rate higher in KRAS wild-type	0.0003
De Roock *et al.* 2008[17]	113	59	Greater reduction in tumor size associated with KRAS wild-type Median OS longer in KRAS wild-type	0.00038 0.02
Tabernero *et al.* 2008[18] and Cervantes *et al.* 2008[19]	48	60	Response rate higher in KRAS wild-type* PFS longer in KRAS wild-type	0.015 0.0475

*cetuximab monotherapy phase. OS, overall survival; PFS, progression-free survival.

and colleagues reported that response rate and progression-free and overall survival were improved in patients with KRAS wild-type tumors compared with patients with KRAS mutant tumors.[12,13]

When tumor samples were analyzed for KRAS status following a recent Phase I trial comparing the safety, pharmacokinetics and pharmacodynamics of an every-second-week schedule of cetuximab with the approved weekly regimen, in 48 patients with previously untreated mCRC, the two schedules were found to be equally effective.[20] Following analysis of the tumor KRAS status of patients in this trial, Tabernero and colleagues reported that, when assessed after receiving 6 weeks of single-agent cetuximab followed by cetuximab in combination with a standard course of FOLFIRI, patients with KRAS wild-type tumors had an ORR of 55% compared with 32% in patients whose tumors had KRAS mutations, demonstrating a 23% increase in response.[18,19] PFS was also longer in patients with KRAS wild-type tumors, which were associated with a 53% lower relative risk of progression than KRAS mutant tumors. In addition, patients with KRAS wild-type tumors showed a higher response rate to single-agent cetuximab (28%) than patients whose tumors harbored KRAS mutations (0%).

In another study,[17] KRAS status was assessed in 113 patients with mCRC that had progressed following irinotecan-based chemotherapy. These patients had been involved in one of four clinical trials (BOND, EVEREST, SALVAGE and BABEL) and had been treated with cetuximab. Median overall survival (OS) was significantly longer in patients with KRAS wild-type tumors compared with patients whose tumors harbored mutant KRAS (43.0 vs 27.3 weeks, p=0.020).[17] The ORR was 41% in the patients with KRAS wild-type tumors compared with 0% in patients with KRAS mutant tumors.

Other studies have yielded similar results, with expression of wild-type KRAS being strongly associated with responsiveness to cetuximab in single-arm studies (Table 1). In the published and reported studies detailed in Table 1, the proportion of patients with mCRC who would be more likely to respond to cetuximab (i.e. those with KRAS wild-type tumors) varies between 57% and 73%. Approximately two-thirds of patients with mCRC could benefit from the addition of cetuximab to chemotherapy.

In addition, initial results have now been reported from randomized, comparative, controlled studies confirming the influence of KRAS status on responsiveness to cetuximab in previously untreated patients with mCRC. Early data from these trials (the CRYSTAL and OPUS studies) from patients in whom KRAS status was evaluable were presented recently at the 44th Annual Meeting of the American Society of Clinical Oncology in Chicago.

Cetuximab plus FOLFIRI (the CRYSTAL study)

This open-label, controlled, multicenter, Phase III trial compared cetuximab plus FOLFIRI with FOLFIRI alone in the first-line treatment of EGFR-expressing (EGFR+) mCRC. A total of 1198 patients with histologically confirmed, unresectable, EGFR+ mCRC, with an ECOG performance status (PS) of ≤2, were randomized 1:1 to receive either cetuximab plus FOLFIRI or FOLFIRI alone. The primary endpoint was PFS, and the secondary endpoints included OS, response rate, disease control rate, quality of life and safety. Initial results from this trial were reported at the 43rd Annual Meeting of the American Society of Clinical Oncology in 2007 in Chicago and at the 14th European Cancer Conference in 2007.[21,22] In the intention-to-treat (ITT) population, the ORR was significantly higher in the cetuximab plus FOLFIRI arm compared with the FOLFIRI arm (47% vs 39%), and the addition of cetuximab to FOLFIRI resulted in a significantly longer PFS compared with FOLFIRI alone, with a hazard ratio (HR) of 0.85 (95% confidence interval [CI] 0.726–0.998), indicating a significant (p=0.048) reduction in the risk of progression of 15% when cetuximab was added to FOLFIRI.

For the retrospective analysis investigating the impact of KRAS status on responsiveness, details of KRAS mutation status were available for 540 (45%) of the 1198 patients in the ITT population: these patients are referred to as the 'KRAS-evaluable population'. The patient, disease and treatment characteristics of the KRAS-evaluable population were representative of the overall ITT population.[23] Among the KRAS-evaluable population, 64% had KRAS wild-type tumors.

In patients with KRAS wild-type tumors, the addition of cetuximab to FOLIFIRI reduced the risk of disease progression by 32% (HR 0.68; 95% CI 0.051–0.934; p=0.017) (Table 2). In patients whose tumors harbored KRAS mutations, cetuximab plus FOLFIRI did not show an additional benefit in PFS compared with FOLFIRI alone. However, adding cetuximab to FOLFIRI significantly increased the ORR in patients with KRAS wild-type tumors (cetuximab + FOLFIRI vs FOLIFIRI, 59% vs 43%, p=0.0025), which is equivalent to an increase of 37% in the ORR. No difference was demonstrated in the ORR between the two treatment arms in patients with tumors expressing KRAS mutations.

Table 2
Impact of KRAS status on responses to cetuximab plus chemotherapy in two randomized comparative trials: **(a)** the CRYSTAL study[23] and **(b)** the OPUS study.[24]

a	CRYSTAL (Phase III)			
	FOLFIRI (A) vs cetuximab + FOLFIRI (B)			
KRAS status	Wild-type		Mutant	
Arm	A	B	A	B
HR for PFS	0.68		1.07	
p value	0.017		0.75	
ORR (%)	43	59	ND	ND
p value	0.0025		0.46	

b	OPUS (Phase II)			
	FOLFOX (A) vs cetuximab + FOLFOX (B)			
KRAS status	Wild-type		Mutant	
Arm	A	B	A	B
Median PFS (months)	7.2	7.7	8.6	5.5
HR	0.57		1.83	
p value	0.02		0.02	
ORR (%)	37	61	49	33
p value	0.01		0.11	

FOLFIRI, folinic acid/5-fluorouracil/irinotecan; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin; HR, hazard ratio; ND, data not disclosed in currently available materials; ORR, overall response rate; PFS, progression-free survival.

Cetuximab plus FOLFOX (the OPUS study)

This randomized Phase II study was conducted in 79 centers in Europe in patients with previously untreated EGFR+ mCRC that was not resectable with curative intent. Patients were randomized 1:1, stratified by ECOG PS (0–1 vs 2), to receive cetuximab plus FOLFOX (FOLinic acid/5-Fluorouracil/OXaliplatin) or FOLFOX alone. The primary endpoint was ORR and the secondary endpoints included PFS, OS and safety. The addition of cetuximab to FOLFOX increased the ORR by 10% compared with FOLFOX alone, and among patients with baseline ECOG PS 0–1, the difference in response rates between the treatment arms was statistically significant and in favor of cetuximab plus FOLFOX.[25,26]

The KRAS-evaluable population in this trial comprised 233 (69%) of the 337 patients in the ITT population: 58% of this population had KRAS wild-type tumors. The general demographic and baseline characteristics of the KRAS-evaluable population were representative of the overall ITT population.[24] In patients with KRAS wild-type tumors, the risk of disease progression was reduced by 43% following treatment with cetuximab plus FOLFOX compared with FOLFOX alone (HR 0.57; *p*=0.016). The addition of cetuximab to FOLFOX increased the ORR in patients with KRAS wild-type tumors by 65% (cetuximab + FOLFOX vs FOLFOX: 61% vs 37%; *p*=0.011). The addition of cetuximab did not have a beneficial impact in patients in this study who had tumors expressing KRAS mutations.

Evidence from other agents

Evidence supporting KRAS status as a predictive factor for responsiveness to agents acting through the EGFR also comes from a recent trial using monotherapy with panitumumab, an IgG2 monoclonal antibody against the EGFR, in patients with chemotherapy-refractory mCRC. In this study, 57% of the patients had KRAS wild-type tumors and, in this subgroup, but not in patients with KRAS mutant tumors, panitumumab monotherapy improved PFS, ORR and OS compared with best supportive care.[27]

Safety of cetuximab in patients with mCRC

The safety and tolerability of cetuximab has been investigated extensively in comparative trials. As a single agent[3,5] and in combination with oxaliplatin- and irinotecan-based chemotherapy in patients with mCRC,[3,4,21,22,25,26,28] treatment with cetuximab is associated with the development of an acne-like rash. The rash occurs in ~80% of patients but is classified as >Grade 2 in only ~10% of patients. Interestingly, the severity of the rash may be correlated with response to therapy.[5,13,29] When compared with chemotherapy alone, adding cetuximab to chemotherapy does not appear to increase the frequency or severity of the adverse events associated with chemotherapy.[3,4,21,22,25,26,28]

Conclusions

There is an ever-increasing body of evidence linking KRAS status with responsiveness to cetuximab. These results indicate that patients with mCRC in which wild-type KRAS is expressed should be offered cetuximab in the first-line setting in combination with the standard chemotherapy regimen of choice. In short, cetuximab adds value to chemotherapy alone, irrespective of the chemotherapy regimen used.

The use of KRAS status as a predictive factor for responsiveness to cetuximab allows therapy for mCRC to be tailored to one important characteristic of a patient's tumor. Hopefully, additional straightforward, accessible, predictive factors will be identified in the future, improving the targeting of therapy in CRC and many other malignancies.

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