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TOPIC HIGHLIGHT

2016 Colorectal Cancer: Global view

Clinical efficacy and drug resistance of anti-epidermal growth factor receptor therapy in colorectal cancer

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Abstract

Colorectal cancer (CRC) ranked third in cancer related death and its incidence has been increasing worldwide. In recent decades important therapeutic advances have been developed in treatment of metastatic CRC (mCRC), such as monoclonal antibodies against epidermal growth factor receptor (anti-EGFR), which provided additional clinical benefits in mCRC. However, anti-EGFR therapies have limited usage due to approximately 95% of patients with *KRAS* mutated mCRC do not response to anti-EGFR treatment. Thus, *KRAS* mutation is predictive of nonresponse to anti-EGFR therapies but it alone is not a sufficient basis to decide who should not be received such therapies because; approximately fifty percent (40%-60%) of CRC patients with wild-type *KRAS* mutation also have poor response to anti-EGFR based treatment. This fact leads us to suspect that there must be other molecular determinants of response to anti-EGFR therapies which have not been identified yet. Current article summarizes the clinical efficacy of anti-EGFR therapies and also evaluates its resistance mechanisms.

Key words: Colorectal cancer; Epidermal growth factor receptor; *KRAS* mutation; Anti-epidermal growth factor receptor antibody; Drug resistance

Core tip: Molecular targeting agents, such as monoclonal antibodies against epidermal growth factor receptor (anti-EGFR), provide additional clinical benefits in metastatic colorectal cancer (CRC). However, anti-EGFR therapies have limited usage due to approximately 95% of patients with *KRAS* mutated metastatic CRC do not response to anti-EGFR treatment. Thus, *KRAS* mutation is predictive of nonresponse to anti-EGFR therapies but it alone is not a sufficient basis to decide who should not be received such therapies because approximately fifty percent (40%-60%) of CRC patients with wild-type *KRAS* mutation also have poor response to anti-EGFR based treatment. This fact leads us to suspect that there must be other molecular determinants of response to anti-EGFR therapies which have not been identified yet. Current article summarizes the clinical efficacy of

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INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in both genders (second in females and third in males)[1]; and it is also ranked third in cancer related death in both genders with approximately 15.1 deaths per 100000[2,3]. While the mortality rate of CRC has been decreasing in Western countries, its incidence has been increasing worldwide, except United States[4]. Despite of decreasing death rates, approximately fifty percent of patients with CRC are diagnosed with metastatic disease in their initial assessments[5].

Several chemotherapeutic agents [*e.g.*, pyrimidine analogs (*e.g.*, 5-fluorouracil), platinum-based antineoplastic agents, and topoisomerase inhibitors] have become available in the past and thus survival rate of CRC patients significantly increased. Also, recently developed molecular targeting agents, such as monoclonal antibodies against epidermal growth factor receptor (EGFR) (*e.g.*, cetuximab and panitumumab)[6,7], provided additional clinical benefits in metastatic CRC (mCRC)[8-10].

In several types of cancer, including CRC, EGFR is overexpressed or amplified. Monoclonal antibodies keep EGFR in an inactive state by binding to and occluding the ligand-binding site of EGFR when the ligand is unbound (acting as competitive antagonists). This leads an inhibition of intracellular signaling pathways of EGFR (RAS/RAF/MAPK and PI3K/PTEN/AKT) that involved in several cellular activities including cell proliferation, motility, invasion, and survival[11].

KRAS, a signal transduction molecule, transduces the signal from ligand-bound EGFR to the nucleus. Prospective randomized trials elucidated that presence of mutation in *KRAS* gene leads to non-response to anti-EGFR based treatment[6-10,12-14]. Therefore, it is highly recommended that *KRAS* mutation status should be known before initiating anti-EGFR based treatment in mCRC patients. Thus, *KRAS* mutation is predictive of nonresponse to anti-EGFR therapies but it alone is not a sufficient basis to decide who should not be received such therapies because almost 60% of CRC patients with wild-type (WT) *KRAS* mutation also have poor response to anti-EGFR based treatment[15]. This fact leads us to suspect that there must be other molecular determinants of response to anti-EGFR therapies which have not been identified yet. Current article summarizes the clinical efficacy of anti-EGFR therapies and also evaluates its resistance mechanisms.

CLINICAL EFFICACY OF ANTI-EGFR ANTIBODY IN MCRC

Both Cetuximab, an IgG1 type chimeric monoclonal antibody, and panitumumab, an IgG2 type fully human monoclonal antibody, induce apoptosis by inhibiting downstream signaling pathways of EGFR (RAS/RAF/MAPK and PI3K/PTEN/AKT). Also, these molecules, especially cetuximab, activate antibody-dependent cellular cytotoxicity which consequently improves their cytotoxic actions and therapeutic effectiveness[16].

The recent published randomized non-inferiority phase Ⅲ study showed median overall survival (OS) was similar in patients with mCRC who treated with panitumumab alone and with cetuximab alone[17]. The incidences of any grade and grade 3-4 adverse events were similar in both treatment groups, however, the incidence of grade 3-4 infusion reaction was lower and grade 3-4 hypomagnesaemia was higher in panitumumab group than in cetuximab group[18]. In some studies, cetuximab and panitumumab have been investigated in combination with FOLFIRI (folinic acid, fluorouracil, and irinotecan) and FOLFOX (folinic acid, fluorouracil, and oxaliplatin) as initial therapy option for treatment of mCRC. And a meta-analysis of these 14 randomized studies concluded that there is a clear benefit to the use EGFR inhibitors in patients with WT *KRAS* mCRC[18]. An updated analysis (CRYSTAL trial) demonstrated that adding cetuximab to FOLFIRI as first-line therapy improves survival in patients with WT *KRAS* mCRC[19]. Also another randomized phase Ⅲ study showed that the combination of panitumumab and FOLFIRI significantly improves progression-free survival (PFS), but not OS, in mCRC patients with WT *KRAS*[9]. Three other trials have evaluated the addition of cetuximab to FOLFOX in first line treatment of patients WT *KRAS* mCRC. In randomized phase Ⅱ OPUS study, combination of FOLFOX and cetuximab was associated with increased response rate and PFS. However, this treatment had no benefit in median OS[12]. In the Medical Research Council (MRC) COIN study, adding cetuximab to oxaliplatin-based chemotherapy in patients with WT *KRAS* mCRC increased response rate with no benefit in PFS or OS[20]. Similarly, another phase Ⅲ study (NORDIC-Ⅶ) showed that cetuximab did not add significant benefit when combined with FOLFOX in treatment of patients with WT *KRAS* mCRC[21]. In contrast to earlier studies, the recent published randomized phase Ⅲ CALGB/SWOG 80405 trial demonstrated that addition of cetuximab to FOLFOX or FOLFIRI chemotherapy was significantly increased PFS and OS in treatment of patients with all RAS-WT mCRC[22]. In the study by Douillard *et al*[23] (the PRIME study), which compared panitumumab plus FOLFOX and FOLFOX alone in mCRC patients with WT *KRAS*/NRAS,

panitumumab plus FOLFOX group showed a statistically significant improvement in PFS and OS.

Based on this knowledge, all patients with newly diagnosed mCRC should be tested for *KRAS* mutation. Also screening of *KRAS* mutations seems essential in mCRC patients to initiate anti-EGFR based treatment. But *KRAS* mutation alone is not a sufficient basis to decide who should not be received such therapies because almost 60% of CRC patients with WT *KRAS* mutation also have poor response to anti-EGFR based treatment[15]. Also 5%-9% of CRC patients have a specific mutation in *BRAF* gene (V600E)[24,25]. But the use of BRAF as a predictive marker for response to anti-EGFR based treatment is unclear. This fact leads us to suspect that there must be other molecular determinants of response to anti-EGFR therapies which have not been identified yet.

MECHANISMS OF RESISTANCE TO ANTI-EGFR TREATMENT

KRAS/NRAS/BRAF mutations

Approximately 40% of CRC patients have mutation in exon 2 of the coding of the *KRAS* gene[26,27]. Prospective randomized studies showed that *KRAS* mutations are predictive of non-response to anti-EGFR based treatment[6-10,12-14]. These studies showed that tumors with a mutation in codon 12 or 13 of exon 2 of the *KRAS* gene are essentially unresponsive to anti-EGFR based treatment. Recent studies demonstrated that mutation in *KRAS* outside of exon 2 and mutation in *NRAS* are also predictive for unresponsiveness to ant-EGFR treatment[23,28]. Recently, a study assessed the superiority of FOLFOX plus panitumumab to FOLFOX alone according to *RAS* (*KRAS* or *NRAS*) or *BRAF* (B-type Raf kinase) mutation status. In that study, 17% of patients with non-mutated *KRAS* exon 2 had other RAS mutation which has been shown to be associated with inferior survival with panitumumab plus FOLFOX treatment[23]. Cetuximab or panitumumab treatments seem to be eligible for selected patients with WT *KRAS* tumors who also have BRAF-WT mutations[29].

BRAF oncogene encodes BRAF protein which is a member of RAS/RAF/MAPK (mitogen-activated protein kinase) pathway[27]. Mutations in *BRAF* and *KRAS* genes are mutually exclusive[30]. Approximately 9% (5%-9%) of patients with CRC have a mutation in *BRAF* gene (V600E)[24,25]. CRYSTAL and PETACC-3 studies demonstrated that patients with BRAF mutation have a worse prognosis than those with the WT tumors[19,31]. However, the use of BRAF as a predictive marker is unclear. CRYSTAL study elucidated that BRAF mutation does not seem to be strong predictive biomarker for the addition cetuximab to FOLFIRI in the first line treatment of WT mCRC[19]. Also, subset analysis of the PRIME study found that BRAF mutation indicates poor prognosis but it may not be predictive of the benefit of adding panitumumab to FOLFOX in the first line treatment of mCRC[8]. Tol *et al*[25] demonstrated that *BRAF* mutation is a negative indicator for prognosis in mCRC patients and in contrast to *KRAS* mutation, this feature is not restricted to the outcome of the cetuximab. In subsequent lines of therapy elucidated that *BRAF* mutation is a marker of resistance to anti-EGFR treatment in the non-first line setting of mCRC[29,32,33].

Vemurafenib is orally administered selective inhibitor of BRAF V600 kinase but using it alone in BRAF–mutated CRC patients results insufficient activity[34]. Studies suggested that feedback activation of EGFR signaling might be responsible of the resistance to Vemurafenib in CRC[35,36]. In a cohort study by Hyman *et al*[37], median PFS and OS did not change with vemurafenib monotherapy or vemurafenib and cetuximab combination therapy in patients with CRC (Table 1).

HYPERACTIVATION OF PI3K-PTEN AXIS

Interestingly, 41% of patients do not have *KRAS* or BRAF mutation, and they do not respond to anti-EGFR treatment[29]. Some studies suggested that anti-EGFR downstream pathways other than RAS/RAF/MAPK [*e.g.*, phosphoinositide 3-kinase/phosphatase and tensin homolog pathway (PI3K/PTEN)], might be responsible for the resistance to anti-EGFR based therapy. It was shown that mutation in PI3KCA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) or loss of PTEN is associated with resistance to anti-EGFR based treatment[38-40]. Tural *et al*[41] investigated the effect of oncogenic activation of the members of EGFR downstream pathways (*e.g.*, PI3K, PTEN and BRAF) on response to anti-EGFR therapy. They have showed that PI3K expression and PTEN loss might be used as predictive to the response to anti-EGFR treatment in mCRC patients with WT *KRAS*. According to this study, BRAF negative, PTEN expressing and PI3K non-expressing CRCs have higher response rate and longer PFS and OS than all others. Most studies evaluated PI3K mutation in response to cetuximab based treatments in CRC patients[38,42-45]. In these studies, *PI3K* mutation has been suggested as predictive of resistance to anti-EGFR-based therapies. On the other hand, the role of PI3K mutation in response is conflict. Perrone *et al*[38] has investigated *PI3KCA* gene mutations in CRC patients and they suggested that mutation in PI3KCA causes resistance to anti-EGFR therapies. Also Prenen *et al*[45] analyzed PI3CA and *KRAS* mutations status in chemo-refractory mCRC patients who treated with anti-EGFR based treatment and they did not determine any correlation between PI3KCA mutation and response to anti-EGFR treatment. Nevertheless, most of studies have suggested that PTEN inactivation is a negative predictor of response to anti-EGFR therapy[38-40]. Bardellie *et al*[46] stated that PI3K expression and PTEN loss are correlated with decreased survival and are predictors of poor response to anti-EGFR therapy. Based on these studies, it is well known that activating mutation in PI3KCA or inactivation of PTEN phosphates

Table 1 Clinical trials of targeted agents in combination with chemotherapy as first-line treatments for metastatic colorectal cancer

Ref.	Year	Population	Patient number	Regimen	Median PFS (mo)	P^1	Median OS (mo)	P^1	Response rate (%)	P^1
CRYSTAL[19]	2009	All	599	FOLFIRI	8.0	0.048	18.6	0.31	38.7	0.0038
			599	FOLFIRI + Cetuximab	8.9		19.9		46.9	
		KRAS WT	350	FOLFIRI	8.4	0.0012	20	0.0093	39.7	< 0.001
		subgroup	316	FOLFIRI + Cetuximab	9.9		23.5		57.3	
		KRAS MT	183	FOLFIRI	7.7	0.26	16.7	0.75	36.1	0.35
		subgroup	214	FOLFIRI + Cetuximab	7.4		16.2		31.3	
OPUS[12]	2009	All	168	FOLFOX4	7.2	0.62	18	0.91	36	0.064
			169	FOLFOX4 + Cetuximab	7.2		18.3		46	
		KRAS WT	97	FOLFOX4	7.2	0.0064	18.5	0.39	34	0.0027
		subgroup	82	FOLFOX4 + Cetuximab	8.3		22.8		57	
		KRAS MT	59	FOLFOX4	8.6	0.0153	17.5	0.2	53	0.029
		subgroup	77	FOLFOX4 + Cetuximab	5.5		13.4		34	
COIN[20]	2011	KRAS WT	367	FOLFOX/XELOX	8.6	0.60	17.9	0.68	57	0.049
		group	362	FOLFOX/XELOX + Cetuximab	8.6		17		64	
		KRAS WT	127	FOLFOX	9.2	0.056	-	-	-	-
		group	117	FOLFOX + Cetuximab	9.0		-		-	
		KRAS WT	240	XELOX	8.0	0.56	-	-	-	-
		group	245	XELOX + Cetuximab	8.4		-		-	
		KRAS MT	268	FOLFOX/XELOX	-	-	14.8	0.8	-	-
		group	297	FOLFOX/XELOX + Cetuximab	-		13.6		-	
NORDIC-VII[21]	2012	All	185	Nordic FLOX (control group)	7.9	-	20.4	-	41	-
			194	FLOX + Cetuximab	8.3	0.31	19.7	0.67	49	0.15
			187	intermittent FLOX + Cetuximab	7.3	NA	20.3	0.79	47	NA
		KRAS WT	97	Nordic FLOX (control group)	8.7	-	22	-	47	-
		subgroup	97	FLOX + Cetuximab	7.9	0.66	20.1	0.48	46	0.89
			109	intermittent FLOX + Cetuximab	7.5	NA	21.4	0.66	51	NA
		KRAS MT	58	Nordic FLOX (control group)	7.8	-	20.4	-	40	-
		subgroup	72	FLOX + Cetuximab	9.2	0.07	21.1	0.89	49	0.31
			65	intermittent FLOX + Cetuximab	7.2	NA	20.5	0.84	42	NA
CALGB/ SWOG[22]	2014	KRAS WT group	578	FOLFIRI or mFOLFOX6 + Cetuximab	10.45	NA	29.93	0.34	-	-
80405 (study is ongoing)			559	FOLFIRI or mFOLFOX6 + Bevacizumab	10.84		29.04		-	
PRIME[8]	2010	KRAS WT	331	FOLFOX4	8.0	0.02	19.7	0.072	48	0.068
		group	325	FOLFOX4 + Panitumumab	9.6		23.9		55	
		KRAS MT	219	FOLFOX4	8.8	0.02	19.3	0.068	40	-
		group	221	FOLFOX4 + Panitumumab	7.3		15.5		40	
Hyman *et al*[37]	2015	BRAF V600	10	Vemurafenib	4.5	-	9.3	-	0	-
		group	27	Vemurafenib + Cetuximab	3.7		7.1		4	
Reidy *et al*[51]	2010	All	23	IMC-A12 (anti-IGF-1R antibody)	5.9	-	5.2	-	0	-
			21	IMC-A12 (anti-IGF-1R antibody) + Cetuximab	6.1		4.5		5	
		KRAS WT	20	IMC-A12 (anti-IGF-1R antibody) + Cetuximab	9.4		10.9		0	
		group								

[1]95%CI. PFS: Progression-free survival; OS: Overall survival; All: All patients group; WT: Wild type; MT: Mutant type; NA: Not available; KRAS: KRAS exon 2, codons 12 and 13; FOLFIRI: Irinotecan, fluorouracil, and leucovorin; FOLFOX: Fluorouracil, leucovorin, and oxaliplatin; XELOX: Capecitabine and oxaliplatin; FLOX: Fluorouracil, leucovorin, and oxaliplatin.

can deregulate PI3K signaling pathway[46]. Two studies demonstrated that PI3KCA mutation and PTEN loss which cause PI3K pathway activation are significant predictors of response to anti-EGFR treatment[38,42]. Also, Tural *et al*[41] indicated that PI3K expression and PTEN loss together are correlated with significantly worse outcome.

HYPEREXPRESSION OR HYPERACTIVATION OF TYPE 1 INSULIN LIKE GROWTH FACTOR RECEPTOR

The type 1 insulin like growth factor receptor (IGF-1R) belongs to the class of tyrosine kinase receptors. IGF-1R functions by activating downstream signaling pathways which include MAPK and PI3K/AKT. Previous studies showed that IGF-1R overexpression results neoplastic transformation of cultured cells[47]. Also IGF-1R overexpression was seen in several types of human tumors[48] and its downregulation has been shown to be able to inhibit the growth of these cells[49]. These findings make IGF-1R an attractive candidate as therapeutic target in anti-tumor therapies. A previous study showed that combination therapy of antibodies against to IGF-1R and anti-EGFR results in further inhibition of CRC cell line growth[50]. A phase Ⅱ study evaluated the safety and the efficacy of human anti-IGF-1R monoclonal antibody

(either alone or in combination with cetuximab) in mCRC patients, and both treatment modalities was reported as insufficient in chemorefractory mCRC patients[51] (Table 1).

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