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

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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 anti-EGFR therapies and also evaluates its resistance mechanisms.
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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)[1-3], and it is also ranked third in cancer related death in both genders with approximately 15.1 deaths per 100000[4,5]. While the mortality rate of CRC has been decreasing in Western countries, its incidence has been increasing worldwide, except United States[6]. Despite of decreasing death rates, approximately fifty percent of patients with CRC are diagnosed with metastatic disease in their initial assessments[7].

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)[8-10], provided additional clinical benefits in metastatic CRC (mCRC)[11-14].

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 to the ligand-binding site of EGFR when the ligand is unbound (acting as competitive antagonists). This leads to the ligand-binding site of EGFR when the ligand is unbound (acting as competitive antagonists). This leads to the ligand-binding site of EGFR when the ligand is unbound (acting as competitive antagonists). This leads to the ligand-binding site of EGFR when the ligand is unbound (acting as competitive antagonists).

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[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[19]. An updated analysis (CRYSTAL trial) demonstrated that adding cetuximab to FOLFIRI as first-line therapy improves survival in patients with WT KRAS mCRC[20]. 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[21]. 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[22]. 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[23]. 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 FOLFIRI or FOLOXIRI 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 FOLFIRI 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 anti-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[29]. 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]. CRYSal 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[31]. Tol et al[32] 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 Prenew 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]. Bardelli 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
can deregulate PI3K signaling pathway\cite{46}. Two studies demonstrated that PI3KCA mutation and PTEN loss which cause PI3K pathway activation are significant predictors of response to anti-EGFR treatment\cite{38,42}. Also, Tural et al\cite{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\cite{47}. Previous studies showed that IGF-1R overexpression results neoplastic transformation of cultured cells\cite{49}. Also IGF-1R overexpression was seen in several types of human tumors\cite{49} and its downregulation has been shown to be able to inhibit the growth of these cells\cite{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\cite{50}. A phase II study evaluated the safety and the efficacy of human anti-IGF-1R monodonal antibody

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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) | Median OS (mo) | Response rate (%) | P1 |
|------|------|------------|----------------|---------|----------------|----------------|-------------------|----|
| CRYSTAL\cite{20} | 2009 | All | 599 | FOLFIRI | 8.0 | 0.048 | 18.6 | 0.31 | 38.7 | 0.0038 |
| | | KRAS WT | 350 | FOLFIRI | 8.9 | 19.9 | 46.9 | | |
| | | subgroup | 316 | FOLFIRI + Cetuximab | 8.4 | 0.0012 | 20 | 0.0093 | 39.7 | < 0.001 |
| | | KRAS MT | 183 | FOLFIRI | 9.9 | 23.5 | 57.3 | | |
| | | subgroup | 214 | FOLFIRI + Cetuximab | 7.7 | 0.26 | 16.7 | 0.75 | 36.1 | 0.35 |
| | | All | 168 | FOLFIRI | 7.4 | 0.62 | 18 | 0.91 | 36 | 0.064 |
| OPUS\cite{21} | 2009 | All | 457 | KRAS WT | 7.2 | 0.064 | 18.5 | 0.39 | 34 | 0.0027 |
| | | subgroup | 97 | FOLFIRI | 8.3 | 0.055 | 21.2 | 0.47 | 53 | 0.029 |
| | | subgroup | 82 | FOLFIRI + Cetuximab | 8.6 | 0.0015 | 17.5 | 0.2 | 53 | 0.029 |
| | | KRAS MT | 59 | FOLFIRI | 8.6 | 0.0153 | 17.5 | 0.2 | 53 | 0.029 |
| COIN\cite{22} | 2011 | KRAS WT | 367 | FOLFIRI | 8.6 | 0.6 | 17 | 0.68 | 57 | 0.049 |
| | | group | 362 | FOLFIRI + XELOX | 8.6 | 0.6 | 17 | 0.68 | 57 | 0.049 |
| | | KRAS WT | 127 | FOLFIRI | 9.2 | 0.056 | - | - | - | |
| | | group | 117 | FOLFIRI + Cetuximab | 9.0 | - | - | - | - | |
| | | KRAS WT | 240 | XELOX | 8.0 | 0.56 | - | - | - | |
| | | group | 245 | XELOX + Cetuximab | 8.4 | - | - | - | - | |
| | | KRAS MT | 268 | FOLFIRI/XELOX | - | 14.8 | 0.8 | - | - | |
| NORDIC-II\cite{23} | 2012 | All | 185 | Nordic FLOX (control group) | 7.9 | - | 20.4 | - | 41 | - |
| | | group | 194 | Nordic FLOX + Cetuximab | 8.3 | 0.31 | 19.7 | 0.67 | 49 | 0.15 |
| | | KRAS WT | 187 | intermittent FLOX + Cetuximab | 7.3 | NA | 20.3 | 0.79 | 47 | NA |
| | | subgroup | 97 | Nordic FLOX (control group) | 8.7 | - | 22 | - | 47 | - |
| | | subgroup | 109 | intermittent FLOX + Cetuximab | 7.9 | 0.66 | 20.1 | 0.48 | 46 | 0.89 |
| | | KRAS MT | 58 | Nordic FLOX (control group) | 7.8 | - | 20.4 | - | 40 | - |
| | | subgroup | 72 | intermittent FLOX + Cetuximab | 9.0 | 0.07 | 21.1 | 0.89 | 49 | 0.31 |
| CALGB/SWOG\cite{24} | 2014 | KRAS WT | 578 | FOLFIRI or mFOLFIOX6 + Cetuximab | 10.45 | NA | 29.93 | 0.34 | 42 | NA |
| | | group | 559 | FOLFIRI or mFOLFIOX6 + Bevacizumab | 10.84 | 29.04 | - | - | - | |
| PRIME\cite{25} | 2010 | KRAS WT | 331 | FOLFIRI | 8.0 | 0.02 | 19.7 | 0.072 | 48 | 0.068 |
| | | group | 325 | FOLFIRI + Panitumumab | 9.6 | - | 23.9 | - | 55 | - |
| | | KRAS MT | 219 | FOLFIRI | 8.8 | 0.02 | 19.3 | 0.068 | 40 | - |
| | | group | 221 | FOLFIRI + Panitumumab | 7.3 | - | 15.5 | - | 40 | - |
| | | Hyman et al\cite{48} | 2015 | BRAF V600 | 10 | Vemurafenib | 4.5 | - | 9.3 | - | 0 | - |
| | | group | 23 | Vemurafenib + Cetuximab | 3.7 | - | 7.1 | - | 4 | - |
| | | Reidy et al\cite{49} | 2010 | All | 23 | IMC-A12 (anti-IGF-1R antibody) | 5.9 | - | 5.2 | - | 0 | - |
| | | group | 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 | - | - | |

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.
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