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Molecular biomarkers of resistance to anti-EGFR treatment in metastatic colorectal cancer, from classical to innovation

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Abstract

Background: Systematic dissection of the EGFR pathway was considered as the best way to identify putative markers of resistance to anti-EGFR therapies. This kind of approach leaves other, less known but by no means less important, putative mechanisms of resistance. We tried to shed some light on these mechanisms of resistance.
Materials and methods: We performed a research through Pubmed database of all published articles highlighting mechanisms of resistance to Cetuximab and Panitumumab based therapies, published in 2000–2012 period.
Conclusions: We reviewed the "classical" molecular factors, extensively analyzed as predictive factors for efficacy to anti-EGFR therapy, such as K-ras, B-raf, and PI3K–mTOR–Akt, focusing on their predictive or prognostic value and on the controversial aspects of the biomarker

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analysis for clinical practice. On the second part we will then move on to other less known molecular markers, for the future understanding of biological mechanisms underlying anti-EGFR therapy resistance, such as non-canonical heterodimer candidates, microRNA, IGF1-IGF1R, HGF-cMET and secondary mutations of EGFR.

Keywords: Anti-EGFR; Biomarkers; Colorectal cancer; Resistance

1. Part 1 – classic

One of the most promising targets for anti-tumour inhibition is the epithelial growth factor receptor (EGFR). This protein is expressed on the cell surface of several different tissues, including tumours arising from gastrointestinal and pulmonary tract. Research focused on the development of drugs (antibodies or oral tyrosine kinase inhibitors) directed against this target. In metastatic colorectal cancer the 2 'most successful' drugs tested and approved are Cetuximab (a IgG3 type chimeric antibody directed against the extracellular portion of the receptor) and Panitumumab (a IgG2 type human antibody directed against the same epitope). The first studies that employed the use of Cetuximab [1], were based on the hypothesis that the drug could be active only on the population of tumours expressing this marker [2,3] and EGFR-negative tumours may still have some kind of tumour shrinkage when treated with this drug [4,5]. Upon the discovery that EGFR evaluation was not able to identify the proportion of patients who had a higher likelihood to response, focus shifted on the other members of the EGFR mediated signalling: the typical pathway consists in activation of different intracellular kinase that are sequentially recruited through phosphorylation, such as Ras-Raf-MEK-ERK family proteins. It should also be noted that another less common way of signal transduction is through activation of PI3K, thus activating the PI3K–Akt–mTOR pathway, crucial for maintaining cell homeostasis and survival.

Studies on K-ras have met with success, at least in identifying a potential marker of resistance.

In this part of the review we will focus on the "classical" molecular factors, extensively (but not always) analyzed as predictive factors for efficacy to anti-EGFR therapy.

1.1. K-ras

K-ras is a member of a superfamily of GTPase proteins which are kinases using intracellular GTP and working via phosphorylation of intracellular proteins, with a particular affinity towards EGFR mediated signalling [6–8]. A mutant K-ras, constitutionally active, could make tumour cells resistant to EGFR inhibition because of the loss of control of the downstream pathway [6–8]. There are several known mutations of K-ras identified in colorectal cancer.

The first confirmatory evidence was the analysis by Amado et al. [9] on patients included in the pilot phase III trial employing Panitumumab + best supportive care (BSC) versus BSC alone [10], proving a longer progression free survival (PFS) for Panitumumab in the unstratified population, maintained in the K-ras wild type (WT) population (12.3 vs 7.3 weeks).

Based on similar analyses (resumed on Table 1), it has been established that K-ras mutation is a solid marker of resistance to anti-EGFR treatment (negative predictive value 93%), so it entered clinical practice for colorectal cancer.

However, not all K-ras mutations seem to be equal.

De Roock et al. [11], among 579 patients, proved significantly better OS (7.6 vs 5.7 months) and PFS (4.0 vs 1.9 months) for patients treated with Cetuximab and harbouring a G13D mutation, stratified for K-ras mutational status.

These data have not been confirmed in similar analysis deriving from the CRYSTAL and OPUS trials [12], presented at the 2011 ASCO meeting, that did not show different outcome for different K-ras mutations.

On these basis, a prospective evaluation of G13D K-ras mutation is warranted before any definitive conclusion can be made for clinical practice.

About other variants of K-ras mutation, published data are lacking. A retrospective analysis of De Roock et al. [13] proved a significantly lower RR for patients with a mutation in codon 61 (but not in codon 146).

In a further experience [14] codon 61 and 146 mutations were analyzed in pre-treated metastatic colorectal cancer patients treated with Cetuximab + Irinotecan. RR in the 87 WT patients was 28%. None of the patients harbouring codon 61 and 146 K-ras mutations achieved a response, while PFS was significantly shorter than WT patients.

Another evaluation of Oliner [15], presented at the 2011 ASCO meeting, seems to question the role of codon 61 mutations as predictor of resistance to Panitumumab, but no significant differences of RR were found between mutated or WT patients.

This report increases the amount of doubts regarding the usefulness of this biomarker in clinical practice.

1.2. N-Ras

One of the hypothesized mechanisms of resistance to anti-EGFR therapy is the mutation of other Ras family members, such as N-Ras.

De Roock et al. [13] evaluated different N-ras gene mutations, considering codon 12, 13 and 61 as potential indicators of mutant gene. N-ras mutant patients (2.6% among 644 patients, all K-ras WT) showed a significantly lower RR than their counterpart N-ras WT (7.7% vs 38.1%). PFS and OS were not statistically different, whereas in the COIN trial [16]