EXPERT OPINION

Dilemma in metastatic colorectal cancer: VEGF versus EGRF targeting

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The modern approach for metastatic colorectal cancer (mCRC) patients is based on the identification of oncogenic pathways, which could be targeted by specific molecules. Vascular endothelial growth factor (VEGF)- and epithelial growth factor receptor (EGFR)-related pathways represent the most important biological mechanisms for cancer development and progression. However, the most significant results by VEGF and EGFR targeting could be achieved through the combination of these drugs with standard chemotherapeutic regimens. These strategies aim to improve the resectability of liver and lung metastases. For those patients who cannot be eligible for metastases resection, a 'continuum of care' has been proposed as the best option. This strategy includes the sequential delivery of various regimens with different targeted drugs. For this reason the choice of the pathway to target, that is, VEGF or EGFR, is not a real dilemma since both these molecules would be targeted during the mCRC natural history. To date, a selection by KRAS mutational status is mandatory to identify those patients with higher probability of benefit from anti-EGFR monoclonal antibodies. In this case VEGF targeting is the only way to choose. New molecules are under evaluation to widen these treatment options.

Keywords: colon cancer, EGFR, target therapies, VEGF

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Long time has passed since the role of various molecular pathways was stated for colorectal cancer (CRC) pathogenesis. Genetic and epigenetic alterations were located in the different steps of colorectal carcinogenesis, as Vogelstein proposed in 1990 [1]. Some genetic mutations seem to prompt a predominant role of particular oncogenes for cancer development and progression, as defined by the 'oncogene addiction' model. On these bases new drugs were developed to target specific molecular pathways. To date, vascular endothelial growth factor (VEGF)-mediated angiogenetic mechanisms and epithelial growth factor receptor (EGFR)-related proliferation are the best studied biological processes in CRC. The former represents a way for the connection between cancer cells and the host, through the stroma in tumor microenvironment. The latter is the main regulator of homeostasis in the intestinal epithelium, but in cancer cells it could turn to constitutive activation by genetic mutations in those genes implicated in its signaling transduction pathway. Three monoclonal antibodies (moAbs) were developed and approved for clinical use to target these phenomena of cancer cell function. Bevacizumab is directed against soluble VEGF-A, and Cetuximab and Panitumumab bind EGFR to block its signaling transduction [2,3].

These moAbs showed limited antitumor activity as single agents in some clinical trials [4,5]. However, an improvement of both tumor response and survival

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endpoints was obtained when combined with backbone chemotherapeutic regimens, including fluoropyrimidines alone or with oxaliplatin or irinotecan [6-9]. A 25-month median overall survival has been overcome since these moAbs were introduced in the treatment strategies for metastatic CRC.

The first-line treatment has always been considered the main setting to evaluate the real efficacy of a particular therapeutic regimen. However, recently the sequential application of different chemotherapy regimens is becoming the main goal for those patients for whom cure could not be achieved. For this reason this approach is usually described as 'continuum of care.' By this perspective the choice of a chemotherapy regimen and a targeted drug to combine with it is not a fundamental matter, since the real aim is to have many different treatments to control metastatic CRC and related symptoms as long as possible.

A recent trial showed the feasibility of continuation of bevacizumab after first-line progression changing the associated chemotherapeutic regimen [10]. New anti-angiogenetic drugs such as aflibercept, a VEGF inhibitor, induced further benefit after first-line treatment with bevacizumab-based regimens [11]. These findings suggest a predominant role of angiogenesis in CRC progression and the possibility to prolong survival benefit in mCRC patients through sequential inhibition of the angiogenetic pathway in the various lines of treatment, above all for those patients with KRAS mutated tumors. We propose that these different strategies could offer more options according to the tumor aggressiveness (i.e., aflibercept for symptomatic patients with earlier progression after first-line bevacizumab; bevacizumab beyond progression for those patients experiencing later progression or with asymptomatic disease).

The choice for a particular targeted drug for combination with chemotherapy, as first-line challenge, becomes relevant just for those patients who need intensive therapy for potentially resectable metastases, tumor-related symptoms, high tumor volume, or high rate of progression [12]. For these cases the anti-EGFR moAbs seem to achieve higher response rates and resection rates than anti-VEGF moAbs when combined with first-line chemotherapy. Anyway these results are more evident in selected than unselected patients, in particular for KRAS mutational status and metastatic number and sites [13]. Even if a selection could be made for patients with a higher probability of efficacy deriving from anti-EGFR moAbs, no studies founded biomarkers for prediction of efficacy induced by bevacizumab [14]. Recently a role as predictive factor of anti-angiogenetic therapy has been recognized to sVEGFR-2 [15]. New methods of selection have been also tested for anti-EGFR moAbs, since KRAS mutations were detected in circulating DNA, yielding an easier way of detection for clinical practice [16,17].

To date, we lack evidence for difference of efficacy between anti-VEGF and anti-EGFR moAbs. All considerations we could report are obtained by extrapolation from various specific clinical trials. Some authors supposed the potential synergism between angiogenesis and EGFR-related pathway. Clinical trials were designed to test the feasibility of a regimen including both chemotherapy, bevacizumab and panitumumab or cetuximab. These triple combinations appeared to be detrimental in mCRC patients [18,19].

Recently, a new interesting philosophical approach has been emerged in the clinical practice scenario: the potential role of anti-EGFR-based therapy rechallenge during the 'continuum of care' of mCRC patients [20]. This clinical choice is based on the hypothesis that the progression after an initial treatment response in wild-type KRAS primary tumors could be due to the selection of a mutated clone, rather than to a late acquisition of a KRAS mutation, based on a sort of 'anti-EGFR-driven mutated genotype acquisition' during therapy. This new approach, if will be confirmed, may further delay the disease progression and improve therapeutic options for mCRC patients.

Even toxicity profile is quite different between these two kinds of targeted agents. Anti-EGFR moAbs are able to induce skin toxicity mainly, since EGFR-targeting is not specific for cancer cells and could affect also cutaneous epithelium. VEGF inhibition can prompt hypertension, proteinuria and hemorrhage or thrombosis. In few cases the adverse effects from both anti-EGFR and anti-VEGF drugs imposed a treatment withdrawal. Rarely these effects were serious or life-threatening. For this reason the differential toxicity profile is not a valid criterion to choose the proper biological drug in mCRC patients.

In conclusion we could propose that the choice of VEGF- or EGFR-targeting agents in mCRC patients does not represent a real dilemma. In fact each combination of a targeted drug with chemotherapy could find a proper location in the overall treatment strategy as a 'continuum of care,' above all if we consider tumor and patient characteristics. For example, mutant KRAS-bearing tumors keep from anti-EGFR moAbs use. So the patients with mutated KRAS can benefit just from the addition of bevacizumab to chemotherapy.

Another particular situation is represented by those mCRC patients with potentially resectable metastases and wild-type KRAS, because anti-EGFR moAbs combined with chemotherapy could achieve higher tumor response rates and subsequently higher probability of respectability. Until a clear evidence is not available through direct comparison between anti-VEGF and anti-EGFR moAbs, the choice for a particular drug in first-line treatment could be based only on physician's experience and deductive considerations from completed clinical trials.

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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