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.

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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 angiogenic 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...
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, and metastatic number and sites [13]. 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**

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Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

8. This study prompted the use of panitumumab in combination with chemotherapy for first-line treatment of metastatic colorectal cancer.
11. A wide review analysis about the landscape of target therapies in metastatic colorectal cancer, including a description of the most important trials and an insight about treatment strategies and continuum of care.
12. This trial is one of the most important highlighting the significant role of bevacizumab in combination with chemotherapy for metastatic colorectal cancer.
16. This study prompted the use of panitumumab in combination with chemotherapy for first-line treatment of metastatic colorectal cancer.
20. This trial’s findings allow to argue a role for rechallenge as a strategy for overcoming acquired resistance to target therapies.

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