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Second-line angiogenesis inhibition in metastatic colorectal cancer patients: Straightforward or overcrowded?

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Contents

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ABSTRACT

Although the number of therapeutic options targeting tumour angiogenesis is becoming increasingly relevant, the question of the optimal choice for second-line anti-angiogenic inhibition in combination with chemotherapy for metastatic colorectal cancer patients remains largely unanswered.

In fact the lack of head to head comparison between consolidated options such as bevacizumab and new treatment alternatives such as aflibercept and ramucirumab makes the selection in the clinical practice challenging, particularly when the patient has already received an anti-angiogenic-based combination up-front.

In the following pages we described the biological scenario validating second-line angiogenesis inhibition in colorectal cancer along with potential mechanism of resistance. We also critically described the available evidence recommending the use of the bevacizumab, aflibercept and ramucirumab in this setting with the final aim to guide the choice in the clinical practice.

1. Second line angiogenesis inhibition: the negation of the reactive homeostasis concept

The term reactive homeostasis is used to describe a reactive compensation to a violent change of the complex network of processes that were present in an enclosed system prior to the introduction of an external factor. Preclinical and clinical data suggest that most of the mechanisms allowing a cancer cell (enclosed system) to escape from the activity of an external factor (chemotherapy agent) might be due to an increased excretion of the drug, mutations in the pharmacological target or apoptotic death of sensitive cancer cells (and their consequential replacement with resistant cells) (Banfalvi, 2014).

Applying this principle to angiogenesis inhibition proves less straightforward mainly as the system itself cannot be considered

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enclosed. Multiple biological determinants are in fact involved, starting from the well-known VEGF-activated pathway to immunological and hypoxia related factors to name few.

In patients-derived xenografts (PDXs) the tumour neoangiogenetic process resulted dependant on endothelial cell transdifferentiation and increased VEGF-VEGFR activity (Bieche et al., 2014). In particular, in colon-derived PDXs, the VEGFR1/FLT concentrations suggested that the xenograft might induce a disturbance in the biological activities undergoing in the stroma.

Investigators also reported that circulating levels of mice VEGF were decreased whereas the concentration of human VEGF-A increased, thus suggesting that an altered production of human VEGF-A by transdifferentiated endothelial cells was also able to suppress the production of VEGF from mice as well.

Sitohy et al. (2012) showed that the VEGF activity was a crucial factor in the vascular transition from pre-existing venules into "mother vessels" (MV) and subsequently into 3 different types of blood vessels, glomeruloid microvascular proliferations (GMPs), vascular malformations (VM) and proper capillaries (Sitohy et al., 2012). When VEGF was withdrawn from the tumour tissue, VM and capillaries tended to remain stable while MVs and GMPs rapidly degenerated and disappeared, thus supporting the idea that VEGF inhibition might be important at the start of the tumour neoangiogenetic process. The Authors hypothesised that the conservation of VM and capillaries might be supported by the presence of a smooth muscle cell wall around the vessels, which is not present in mother vessels and GMPs.

The biological consequences of sustained VEGF inhibition on determinants not directly implied in the neoangiogenetic process, such as immunological-related factors, are still not well defined, although likely to become increasingly relevant in the near future.

Findings from an analysis conducted in colon cancer buds deriving from knockout mice treated with a VEGF inhibitor suggested in fact a significantly decreased concentration of tumour infiltrating lymphocytes (predominantly CD8+ and CD4+) along with a significantly decreased concentration of anti-tumoural cytokines such as interleukin-6/10 (Yang et al., 2015).

Angiogenesis inhibition is a continuously transforming process. In a study by Miyazaki et al. (2014), the Authors analysed the pattern of gene expression for colorectal cancer PDXs after sustained treatment with bevacizumab (Miyazaki et al., 2014). In this analysis the administration of bevacizumab was able to induce mitotic arrest after 14 days of treatment, but the tumour xenograft rapidly developed resistance with tumour regrowth 35 days after the start of treatment. Tumour tissue from resistant PDXs revealed a high HIF-1alpha expression, high concentration of aldeide-dehydrogenase-1 and high stanniocalcin-2 gene (STC2) expression.

Other data focused on different biological changes induced by VEGF inhibition that may have a potentially interesting impact on future treatment strategy (Xu et al., 2013; Tomida et al., 2015).

In a preclinical model bevacizumab-resistant cancer cells expressed persistent mitochondrial defects making them particularly vulnerable to glycolysis inhibitors. Observations in bevacizumab-treated PDXs showed in fact, along with a loss of expression of mythocondrial protein, also a significantly higher production of HIF-1, with a global increase in the glycolytic activity (Xu et al., 2013).

Furthermore Tomida et al. (2015) demonstrated that the colon cancer cell line HCT116 developing resistance to bevacizumab treatment showed an increased production of VEGFR1, VEGFR2 and PlGF (Tomida et al., 2015).

More interestingly in the intrinsically bevacizumab resistant HT-29 colon cancer cell line, cross-reacting drugs directed against the VEGF-mediated pathway such as Nindetanib, could still maintain some activity (Mesange et al., 2013). HT-29 PDXs exhibited at least 4-times fold increase in expression of VEGF compared with control PDXs.

Globally these data seem to indicate that sustained VEGF-A inhibition achieved by the use of bevacizumab may be unable, in the long term, to determine a significant tumour shrinkage and does convey a series of biological changes in the stromal-tumour interactions that are mainly derived from a hypoxic insult (Scartozzi et al., 2012a,b; Del Prete et al., 2015; Silvestris et al., 2015; Giampieri et al., 2014; Faloppi et al., 2014).

Preclinical data also suggest that VEGF continues to be expressed during tumour progression and that a prolonged (beyond-progression) exposure to anti-angiogenic agents could delay tumour growth (Berges and Benjamin, 2003). Results from different studies indicate that longer duration of bevacizumab treatment may in fact results in an improved patients benefit as well as early discontinuation following first line chemotherapy could results in "tumour rebound" or emergency of a more aggressive disease progression. According to this biological scenario anti-angiogenic treatment might continue to be effective even when tumour cells develop resistance to chemotherapy while interruption of the anti-angiogenic inhibition could prove deleterious (Bagri et al., 2010; Giantonio, 2009).

2. Bevacizumab second-line and beyond progression: first come, first served?

The combination of bevacizumab (an anti vascular endothelial growth factor A, VEGF-A, monoclonal antibody) and standard chemotherapy is a cornerstone therapeutic option in the first line treatment of metastatic colorectal cancer patients (Hurwitz et al., 2004) (Table 1). Unfortunately, drug resistance develops, after initial benefit, through a variety of mechanisms that have been previously discussed.

Two retrospective studies, BRiTE (Grothey et al., 2008) and ARIES (Bendell et al., 2012), have suggested that continuing bevacizumab beyond progression switching to standard second-line chemotherapy could improve both progression-free and overall survival. Based on these data, several prospective studies were designed to define its role in second line of treatment.

Giantonio et al. first investigated the role of bevacizumab in patients with previously treated metastatic colorectal cancer in the randomized phase III E3200 study. Eight hundred-twenty nine metastatic colorectal cancer (CRC) patients previously treated with fluoropyrimidine and irinotecan were randomly assigned to receive one of three treatment options: oxaliplatin, fluorouracil and leucovorin (FOLFOX-4) with Bevacizumab (at the dose of 10 mg/kg every two weeks), FOLFOX4 without bevacizumab or bevacizumab alone. The arm containing bevacizumab alone was closed early after an interim analysis showed a worse outcome than the others arms. The primary end-point of the study was overall survival (OS). Secondary end-points were progression free survival (PFS), response and toxicity. Combining Bevacizumab with FOLFOX4 resulted in a statistically significant improvement in OS with a median survival of 12.9 months compared with 10.8 months for FOLFOX4 alone (HR = 0.75; p = 0.0011). The median PFS for patients treated with bevacizumab plus chemotherapy was 7.3 months compared with 4.7 months for those receiving chemotherapy alone (HR = 0.61; P < 0.0001). Twenty-three percent of patients in the FOLFOX4 + bevacizumab arm obtained a RECIST response to therapy compared with 8.6% of patients in the FOLFOX alone arm (p < 0.0001) (Giantonio et al., 2007).

More recently, two large randomized trials have being conducted with the aim to investigate the activity of anti angiogenic therapy after fist line progression. The phase III ML18147 study explored the role of continuing bevacizumab, in combination