

Novel anti-angiogenic agents for colorectal cancer. Are we moving on?

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Introduction

Tumours depend greatly on blood supply to grow, spread and metastasise. It has been proposed, for a long time now, that angiogenesis and neo-vasculature development are present in tumours^[1,2]. Angiogenesis is subject to regulation by a number of pro-angiogenic growth factors such as the vascular endothelial growth factors (VEGFs), angiopoetin, platelet derived growth factor (PDGF), placental growth factor (PIGF) and others, which are counteracted by proangiogenic growth factors such as angiostatin, transforming growth factor-beta (TGF- β) and others^[1,3]. Among those growth factors, the most studied and associated with tumour growth and neo-angiogenesis is the family of the vascular endothelial growth factor (VEGF), which includes VEGF-A (the archetypal member, often called as VEGF), placental growth factor (PIGF), VEGF-B, VEGF-C, and VEGF-D (known also as c-Fos-induced growth factor, FIGF), and the viral VEGF-E. These growth factors exert their biological function through the VEGF transmembrane receptors VEGFR-1, -2 and -3. In particular, VEGF binds to VEGFR-1 and -2, VEGF-B and PIGF only to VEGFR-1, VEGF-C and VEGF-D to VEGFR-2 and -3^[4-8].

Based on this preclinical evidence, novel agents targeting the tumour vasculature at various levels (antibodies binding growth factor ligands or blocking their receptors, small molecules inhibiting phosphorylation of tyrosine kinase of growth factors, multi-kinase inhibitors) have been developed and tested in clinical trials over the last decade (Figure 1)^[9-13].

A lot of agents have been tested, but until recently only the recombinant humanised monoclonal antibody against the vascular endothelial growth factor-A (VEGF) bevacizumab had showed clinical efficacy in advanced colorectal cancer (CRC), improving response rate, progression free and overall survival as demonstrated in many trials in the first or second line treatment^[14,15]. This benefit was present only when bevacizumab was added to a chemotherapy agent. The first randomised, placebo controlled clinical trial, that led to approval of this agent by the authorities, was conducted in 2004 by Hurwitz *et al* who showed that addition of bevacizumab to irinotecan, 5-fluorouracil and leucovorin (IFL) regimen in the first line CRC setting improved survival rate by almost 5 months^[16]. Subsequently, other studies have confirmed the efficacy of bevacizumab in various combinations with irinotecan, oxaliplatin and fluoropyrimidines (5-fluorouracil or capecitabine) in the first or second line setting^[17-19]. Unfortunately, the majority of patients do not show benefit from the addition of this antibody, and significant research on the potential mechanisms of resistance or escape from bevacizumab actions is being undertaken. One of the hypotheses suggested that upregulation of other angiogenic proteins such as PIGF

or VEGF-B might occur (especially secondary to VEGF-A blockage by bevacizumab) and might maintain the stimulus to VEGF signalling pathway. Since 2004, a large number of studies testing various anti-angiogenic agents (antibodies or small molecules) on metastatic colorectal cancer were conducted with disappointing results, until recently that two novel agents targeting vasculature have showed some benefit on metastatic CRC. (Table 1)

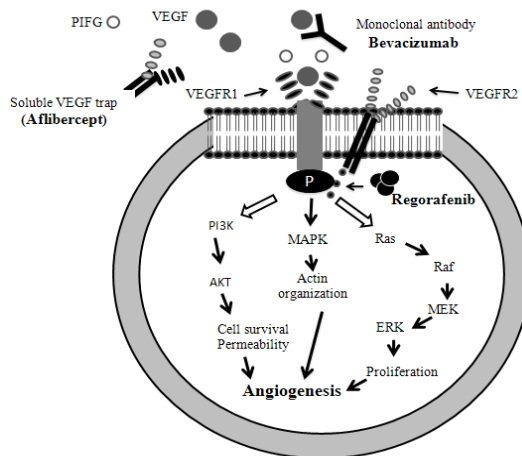


Figure 1. The VEGFR pathway and targets of treatment

Table 1. Effective anti-angiogenic biological agents tested in phase III studies in advanced colorectal cancer

Agent	Mode of action	Approved indication	Added survival benefit (mo)
Bevacizumab	Recombinant monoclonal antibody against VEGF	- 1 st line + CT	PFS: 4.4 OS: 4.7
		- 2 nd line + CT	
Aflibercept	Fusion protein consisted from the IgG1 portions of VEGFR1 & 2 that binds circulating VEGF (VEGF trap)	2 nd line + FOLFIRI	PFS: 2.23 OS: 1.44
Regorafenib	Multi kinase inhibitor (mainly VEGFR1-2-3, TIE2, PDGFR, c-KIT, RET)	3 rd line treatment as monotherapy	PFS: 0.2 OS: 1.4

Abbreviations: CT; chemotherapy, OS; overall survival, PDGFR; platelets derived growth factor receptor, PFS; progression free survival, TIE2; tyrosine kinase with immunoglobulin and EGF homology domain 2, VEGF; vascular endothelial growth factor

The first one, aflibercept (AVE0005), a fully humanized recombinant fusion protein, fuses the extracellular domain 2 from VEGFR-1 and the extracellular domain 3 from VEGFR-2, with the constant region of the human immunoglobulin G1 (IgG1). This fusion antibody mainly binds the circulating VEGF-A ligand, with higher affinity than the native VEGF receptors, and secondly traps the ligands VEGF-B, and PlGF 1 and 2 which are often upregulated in colon cancer inhibiting thus VEGF pathway and angiogenesis [20]. Following encouraging results from phase II clinical studies, a phase III double blind randomized placebo controlled study on second line colorectal cancer treatment tested the benefit of aflibercept in combination with FOLFIRI (5-fluorouracil, leucovorin and irinotecan) regimen [21]. The study recruited 1226 patients who were randomized to either FOLFIRI plus aflibercept (n=614) or FOLFIRI plus placebo (n=612). The primary endpoint of the study was overall survival and secondary endpoints were progression free survival and response rate. The experimental arm was better for median OS (13.50 months versus 12.06 months, $p=0.0032$), PFS (6.90 versus 4.67 months, $p=0.00007$) and overall response rate (19.8% versus 11.1%, $p=0.0001$). As far as toxicity was concerned, more patients on the aflibercept arm experienced grade 3 and 4 toxicities, especially diarrhea, asthenia, mucositis, infections, hypertension, abdominal pains, neutropenia and proteinuria which led to more treatment discontinuations than the placebo group (26.6%

versus 12.1%)^[21]. An important observation was that the benefit from aflibercept was irrelevant to whether patients had previously received bevacizumab or not. This somehow confirms that other upregulated and important for tumour growth and angiogenesis molecules (such as VEGF-B and PlGF) confer resistance to bevacizumab and their inhibition is associated with clinical benefit.

The second novel agent, that recently attracted attention in advanced CRC, is regorafenib (BAY 73-4506), an oral multikinase inhibitor of the extracellular vascular receptors VEGFR1-3, the stromal platelet-derived growth factor receptor- β (PDGFR-beta) and fibroblast growth factor receptor 1 (FGFR-1) as well as some oncogenic cytoplasmic kinases (KIT, RET, B-RAF). Regorafenib was tested on the CORRECT trial (Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy), an international, multicenter, randomized, double-blind study that enrolled 760 patients with mCRC refractory to standard treatments. Patients received 160 mg of regorafenib (or placebo) once a day for three weeks followed by one week off plus best supportive care (BSC). The primary endpoint of the study was overall survival whereas secondary endpoints included progression-free survival (PFS), response rate and disease control rate (DCR). The study's results were recently announced at the 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Symposium, after an early closure of the study following an interim review by an Independent Data Monitoring Committee which recommended unblinding of the study based on significant difference on survival between the two study arms. Indeed, the experimental arm (regorafenib plus BSC) showed a statistically significant improvement in median overall survival (OS) by 29% or 1.4 months (6.4 versus 5.0 months) (HR=0.77, $p=0.0052$) compared to placebo plus BSC. Secondary endpoints were also met with a median PFS of 1.9 months in the regorafenib arm versus 1.7 months in the placebo arm (HR=0.49, $p<0.000001$), and DCR of 44.8% versus 15.3% respectively, whereas response rate was very low in both arms (1.0% and 0.6%). The toxicity profile of this agent was similar to the other two aforementioned antivasular drugs with asthenia, hypertension, anorexia, rash but also diarrhoea, mucositis and hand-foot syndrome being the commonest but manageable side effects^[22].

Based on the above findings, one could be pleased with the fact that many years after the success of bevacizumab and following many unsuccessful trials on novel anti-angiogenic agents, we have large randomized studies providing evidence of efficacy of new drugs on the second line and refractory CRC. There are several positive points that one could take out from these two recent studies. Most importantly, the hypothesis that multiple molecular events take place simultaneously on the cellular level explains the reasons why aiming at a single aberration or target (as with bevacizumab) fails to provide very positive clinical results, and why agents targeting multiple molecules (such as aflibercept and regorafenib) show some efficacy, in previously treated patients, even with an anti-vascular agent. Furthermore, the efficacy of these novel drugs in second-on metastatic setting where tumors are particularly resistant and the disease less controlled, allows some optimism that testing in the first or second line CRC and in various combination might be more effective. Of course, at some point these agents will have to test their strengths against bevacizumab and then we will be able to draw conclusions regarding the benefit of targeting upfront molecules at different levels of the pathway, in naïve patients, rather than doing it when the disease has somehow become resistant.

Nonetheless, in the current times of financial restraint, survival benefits by one to two months using these very expensive drugs raise doubts about the clinical significance and meaningfulness and the real impact on the natural course of an incurable disease. Of course, this very important aspect will be taken into account before authorities' give full approval of these two agents in everyday practice. In conclusion, now more than ever biomarkers of efficacy of anti-vascular agents are needed in order to identify those patients who might benefit the most and thus improve our results but also keep the cost at reasonable levels. The translational challenges on this area remain unmet and exciting and more research is worth pursuing by both industry and scientists.

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