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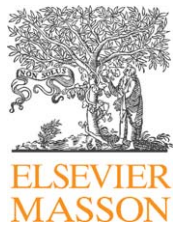

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REVIEW

Targeted biotherapy in metastatic colorectal carcinoma: Current practice

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Cetuximab

Summary Targeted therapy has become an indispensable tool in the management of metastatic colorectal cancer (mCRC). The combination of monoclonal antibodies with conventional polychemotherapy has proven its efficacy as the median overall survival now exceeds 24 months: these novel molecules act by targeting circulating vascular endothelial growth factor (VEGF) and the receptor of epidermal growth factor (EGFR). At the present time, no factor has been identified to predict the efficacy of bevacizumab, an inhibitor of circulating VEGF. On the other hand, mutation of the KRAS oncogen has been proven to be a factor of non-response, or even of deleterious response to the use of EGFR, therefore limiting its use to patients whose tumors bear the wild type KRAS oncogen. Treatment toxicity for these molecules is moderate, specific, and is not cumulative with chemotherapy-related toxicity. On the other hand, combined targeted therapy (association of several targeted therapy drugs) has not been shown to be of any benefit. Other biotherapies continue to be developed, but there is not yet a consensus of how to best target the tumor nor which anti-tumoral molecules to use in the treatment of mCRC.

Introduction

With 37,000 new cases per year, colorectal cancer (CRC) is the third most frequent cancer, and the second leading cause of mortality in France [1]. One out of four CRC are already metastatic at the time of initial diagnosis. Medicosurgical management of mCRC has undergone radical changes in the last few years, essentially because of the development of targeted therapy or biotherapy. Biotherapy has clearly shown its efficacy in controlled randomized trials. Recent data also suggest that the use of these biotherapies could increase the rate of secondary resectability of hepatic metastases (for metastases limited to the liver) and increase overall survival (OS). Two molecular classes of drugs have

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been validated in the treatment of mCRC in combination with chemotherapy. Both are monoclonal antibodies, each with a specific target. Bevacizumab (BV) targets the angiogenesis needed for tumor growth by inhibition of the vascular endothelium growth factor (VEGF) pathway. Cetuximab (Cmab) and panitumumab (Pmab) inhibit the epidermal growth factor (EGF) pathway by acting on its receptor (EGFR). These molecules are used today at several stages of therapeutic strategies for the treatment of mCRC but their addition to the therapeutic armamentarium raises questions as to the medical economic consequences tied to their increasing use. It therefore seems important to define the predictive factors of response to these molecules in order to identify those patients who would most benefit from biotherapy.

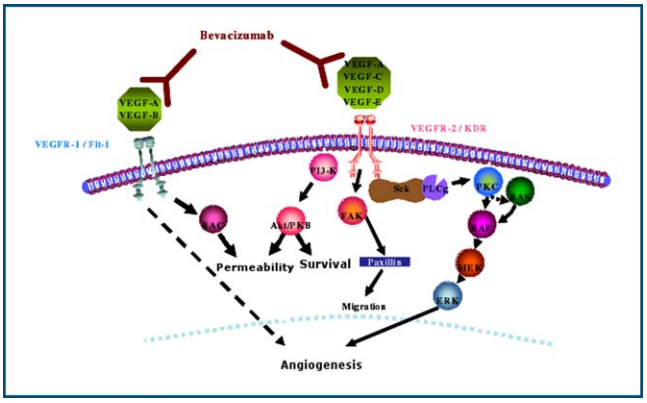

Figure 1. Mode of action of bevacizumab.

Anti-VEGF targeted therapy: bevacizumab (Avastin®)

Mechanisms of action of anti-VEGF

BV is a recombinant humanized and chimeric IgG1 type monoclonal antibody, directed against all the isoforms of the pro-angiogenic peptide VEGF. BV is partly human (93%) and partly murine (7%) in composition. Its half-life is 18 to 21 days. VEGF is a soluble glycoprotein implicated in tumor neoangiogenesis. This glycoprotein is indispensable for the proliferation, survival and migration of endothelial cells. VEGF binds to the Flt-1 (VEGFR-1) and KDR (VEGFR-2) receptors located on the surface of endothelial cells. The mechanism of action of BV is based on the inhibition of the ligand between VEGF and its surface receptors on endothelial cells of the tumor neovessels; their survival is VEGF-dependent. Blocking the binding to the VEGF ligand on these receptors leads to vessel involution by inhibition of the signal transduction pathway (Fig. 1).

Clinical studies of anti-VEGF

1st line treatment

BV is the first targeted therapeutic agent shown to be effective in association with bolus 5-fluorouracyl/leucovorin (5-FU/LV), compared with 5-FU/LV-placebo, leading to a statistically significant increase in progression-free survival (PFS) (9.2 vs. 5.5 months), albeit without statistically significantly increased OS (16.6 versus 12.9 months) [2]. Consequently, this trial was completed by a similar study, comparing combined irinotecan-5 fluorouracyl (IFL)-BV vs. IFL-placebo showing a highly significant increase in OS in the BV treated arm (20.3 versus 15.6 months, $P < 0.001$) [3]. Results were confirmed by the BICC-C study, evaluating the association FOLFIRI-BV versus FOLFIRI-placebo, with a median survival rate of 28 months, and a 63% response rate in the group treated with BV [4]. Lastly, BV combined with oxaliplatin-based chemotherapy showed a significant increase in PFS (9.4 versus 8.0 months, $P = 0.0023$) but, without statistically significant improvement in OS (21.3 vs. 19.9 months) [5] (Table 1).

2nd line and later treatment

BV has been shown to be effective in a study comparing FOLFOX-placebo with FOLFOX-BV in patients with progressive disease who had undergone 1st line chemotherapy with irinotecan; one study showed that this strategy led to significantly increased OS: 12.9 versus 10.8 months [6]. This study led to recommendation of BV in combination with 2nd line chemotherapy for patients who had failed to benefit from 1st line therapy. Beyond 2nd line therapy, the introduction of BV has not shown any efficacy according to a phase II study comparing 5FU-BV with 5FU-placebo after failure with FOLFOX and FOLFIRI [7].

Toxicities

The profile of BV-related toxicity relates to its anti-angiogenic mechanism of action. BV can induce severe complications in up to 10% of patients, most notably arterial hypertension requiring antihypertensive medication; this is usually reversible when BV is discontinued. Other complications include digestive tract perforation (especially from large tumors left in situ, macronodular peritoneal carcinomatosis, or digestive tract endoprotheses), arterial and venous thromboembolic complications, hemorrhage, and delayed healing. Notwithstanding the specter of increased cardiovascular risk in patients over 65, the more recent studies, and in particular, an analysis pooling two controlled studies versus placebo [2,3], were unable

Table 1 Bevacizumab: results of 1st line treatment of metastatic colorectal cancer.

Studies 1st author (year)	Protocols	OR (%)	PFS (months)	OS (months)
Hurwitz (2004)	IFL-BV vs. IFL	44.8 vs. 34.8	10.6 vs. 6.2	20.3 vs. 15.6
Kabbinavar (2005)	5-FU/LV-BV vs. 5-FU/LV	34.1 vs. 24.5	9.2 vs. 5.5	16.6 vs. 12.9 (ns)
Fuchs (2008)	Folfiri-BV vs. Folfiri	63 vs. 41	—	28.0 vs. 19.2
Saltz (2008)	Folfox/Xelox -BV vs. Folfox/Xelox	38 vs. 38 (ns)	9.4 vs. 8.0	21.3 vs. 19.9 (ns)

OR: objective response; PFS: progression free survival; OS: overall survival; ns: not statistically significant; BV: bevacizumab; IFL: association irinotecan + 5-fluorouracyl; 5-FU/LV: association folinic acid + 5-fluorouracyl ; FOLFIRI: association irinotecan + 5-fluorouracyl ; FOLFOX: association oxaliplatin + 5-fluorouracyl ; XELOX: association oxaliplatin + xeloda.