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Angiogenesis inhibition in the second-line treatment of metastatic colorectal cancer: A systematic review and pooled analysis

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ABSTRACT

The last two decades have seen intensive efforts devoted to the development of compounds that target angiogenesis for the treatment of metastatic colorectal cancer (mCRC). In this review, we describe supporting evidence and ongoing development of angiogenesis inhibitors in the second-line treatment of mCRC, and summarize relevant randomized trials to help therapeutic decision-making in daily practice.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide after lung and breast cancer, with 1.4 million new cases per year [1]. Surgery remains the treatment of choice for early-stage CRC and for oligometastatic disease; however, approximately one quarter of patients present with metastatic disease at diagnosis, and another quarter eventually develop metastases during the course of their disease [1,2]. For the majority of patients with metastatic CRC (mCRC) not amenable to curative-intent resection (or ablative procedures), systemic chemotherapy remains the only possible treatment [2].

The advent of oxaliplatin and irinotecan in the 1990s allowed the design of potent combination regimens using a backbone of 5-fluorouracil (5-FU) and folinic acid, as well as other fluoropyrimidines (eg, S-1, capecitabine). Many of these regimens, notably FOLFOX (folinic acid/5-FU/oxaliplatin), FOLFIRI (folinic acid/5-FU/irinotecan), XELOX (capecitabine/oxaliplatin), XELIRI (capecitabine/irinotecan), and FOLFIRINOX/FOLFOXIRI (folinic acid/5-FU/oxaliplatin/irinotecan) are now widely used to treat mCRC [3].

Molecular targeted agents have also been integrated in every treatment line in mCRC with two distinct drug classes approved to date: (1) monoclonal antibodies directed against the epidermal growth factor receptor (EGFR), namely, cetuximab and panitumumab; and (2) agents with antiangiogenic properties including bevacizumab, aflibercept, regorafenib, and ramucirumab. Assessment and approval of EGFR inhibitors was based on the high prevalence of EGFR overexpression leading to frequent EGFR-RAS-RAF-MAPK pathway activation in mCRC [3]. EGFR overexpression subsequently proved to be irrelevant for predicting EGFR inhibitor efficacy in mCRC, contrary to KRAS and NRAS mutations, which have been shown to predict the inefficacy of these targeted agents [3]. The second class of molecularly targeted agents—those targeting angiogenesis—have primarily focused on the family of vascular endothelial growth factors (VEGF), notably VEGF-A, a key effector of tumor angiogenesis, and the structurally related VEGF-B, -C, and -D, as well as placental growth factor PlGF that activate cellular receptors such as VEGFR-1, -2, and -3 to drive angiogenesis [4]. Blocking the VEGF pathway not only can alter the tumor vasculature but it may also improve the delivery of chemotherapy [5]. The addition of an antiangiogenic agent to cytotoxic chemotherapy has proved beneficial in terms of objective response rate (ORR), progression-free survival (PFS), and/or overall survival (OS) in various cancers, including mCRC [6].

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved four agents targeting angiogenesis for the treatment of mCRC. The first approved agent was bevacizumab, a humanized monoclonal antibody that targets solely VEGF-A [7,8] (Table 1). Initially approved by the FDA in 2004, bevacizumab is used in both first- and second-line settings in mCRC, in combination with systemic chemotherapy

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Table 1
Antiangiogenic agents evaluated in completed randomized trials in the second-line treatment of patients with mCRC.

Drug	Class	Target	Trials
Bevacizumab	Monoclonal antibody	VEGF-A	E3200, TML (ML18147), BEBYP, HORIZON I, A406103, M10-300, SPIRITT, PRODIGE 18
Aflibercept	Peptide-Fc fusion protein	VEGF-A/B, PlGF	VELOUR
Ramucirumab	Monoclonal antibody	VEGFR-2	RAISE, I4Y-IE-JCDB
Icrucumab	Monoclonal antibody	VEGFR-1	I4Y-IE-JCDB
Vatalanib	Tyrosine kinase inhibitor	VEGFR-1/2/3	CONFIRM 2
Regorafenib	Tyrosine kinase inhibitor	VEGFR-2/3, TIE-2, KIT, RET, BRAF	LCCC 1029
Axitinib	Tyrosine kinase inhibitor	VEGFR-1/2/3, c-KIT, PDGFR	A406103
Linifanib	Tyrosine kinase inhibitor	VEGFR-1/2/3, PDGFR-α/β, c-KIT, CSF-1R, FLT-1/3/4	M10-300
Cediranib	Tyrosine kinase inhibitor	VEGFR-1/2/3	HORIZON I
Trebananib	Peptide-Fc fusion protein	Angiopoietins-1/2-TIE-2 receptor interaction	2007-0307

VEGFR = vascular endothelial growth factor receptor; PlGF = placental growth factor; KIT = mast/stem cell growth factor receptor (SCFR) = also known as proto-oncogene c-Kit; RET = rearranged during transfection; PDGFR = platelet-derived growth factor receptor; CSF-1R = colony-stimulating factor 1 receptor; FLT-1/3/4 = fms like tyrosine kinase 1/3/4; TIE-2 = tyrosine kinase with immunoglobulin and EGF homology domains; TML = Treatment through Multiple Lines.

[9,10]. In 2012, aflibercept, a recombinant fusion protein with receptor components of VEGFR-1 and VEGFR-2 that binds not only VEGF-A but also VEGF-B and PlGF, was approved in the second-line setting after failure of an oxaliplatin-based regimen [11]. Regorafenib, a multi-kinase inhibitor that inhibits angiogenesis (VEGFR 2/3, TIE-2), growth, proliferation, and the mutant oncogenic kinases KIT, RET and B-RAF (BRAF), as well as a diverse group of other kinases, demonstrated PFS and OS benefit over best supportive care alone in patients with mCRC who had progression of their disease after having been treated with all standard therapies. Based on this, regorafenib received regulatory approval in 2012 in the United States and 2013 in Europe [12]. Finally in 2015, ramucirumab, a fully human monoclonal antibody that specifically targets the VEGFR-2 ligand-binding domain, was approved in the second-line setting based on the results of the RAISE study [13].

The advent of more active cytotoxic drugs and combination chemotherapy regimens and the incorporation of molecular targeted agents, along with the advances in surgery, ablative procedures for resectable metastases and better end-of-life care, have all combined to improve the outcomes for patients with mCRC. For example, 5-year OS of mCRC patients rose from 3% in 1995 to up to 30% in 2016 [14]. Therefore, an increasing proportion of patients will receive multiple lines of therapy. For instance, it is estimated that 75%–85% of mCRC patients will require (and be fit for) second-line treatment [15]. Because each treatment line may impact OS, and because patient's access to all active drugs is thought by some to be crucial in mCRC [16], it is particularly important to determine the best treatment sequence. As such, second-line therapy remains an intensive field of therapeutic development.

The question of the optimal targeted agent to combine with second-line chemotherapy remains under active investigation. Two meta-analyses of randomized controlled trials have been recently published [17,18]. Both confirmed the superiority of a combination of a targeted agent with chemotherapy over chemotherapy alone in the second-line setting in terms of ORR, PFS, and OS. Interestingly, in both meta-analyses, antiangiogenic agents tended to be associated with ORR, PFS, and OS benefits, while EGFR inhibitors tended to improve ORR and PFS, but not OS, compared to control. As an example in the FIRE-3 study, patients benefited more from the therapeutic sequence FOLFIRI-cetuximab then FOLFOX-bevacizumab than from the therapeutic sequence FOLFIRI-bevacizumab then FOLFOX-cetuximab [19].

In this review, we will focus on angiogenesis blockade in the second-line treatment of mCRC, and summarize the data that can help in making clinical decisions.

2. Materials and methods

2.1. Search strategy

We searched the MEDLINE and Cochrane databases through November 2016 to identify relevant published randomized phase II and III studies. Search terms included "colorectal neoplasms" and "antineoplastic combined chemotherapy protocols" and/or "monoclonal antibodies" as MeSH terms, and "administration and dosage", "antagonists and inhibitors", "therapeutic use", "drug therapy", and "therapy" as subheadings. Proceedings of the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) annual scientific meetings were searched for by hand from December 2000 to November 2016. No restriction on language was made. Abstracts were included.

2.2. Trial selection and data extraction

Two authors independently reviewed titles and abstracts and agreed on articles to be retrieved. Discrepancies or uncertainties regarding the eligibility of a trial were discussed with a third investigator and final consensus was made. Registered randomized controlled trials evaluating antiangiogenic agents in the second-line treatment of mCRC, for which OS and/or PFS was reported with available hazard ratios (HRs) and confidence intervals (CIs) were eligible for this study.

The following data were extracted: first author, trial name, regimen (experimental/control arm), accrual period, primary endpoint, numbers of patients in each arm, median follow-up duration, median OS and PFS, HRs and CIs for OS and PFS, deaths, and disease progression events.

2.3. Statistical analysis

All of the analyses were realized retrospectively on summarized data and unadjusted HRs for OS and PFS for each publication when available. Some trials evaluated two doses of the same antiangiogenic agent [20,21] or two distinct antiangiogenic agents [22], but used the same control arm for the comparisons. Thus, for these trials in which the control arm was taken into account twice, the weight of each comparison was reduced according to a correction factor equal to the number of events observed in the trial (three arms) divided by the number of events taken into account in the analysis (four arms). When the number of PFS or OS events was not available, the correction factor used was the same as the one used for the other survival endpoint. This correction resulted in an increase in the width of the CI for the estimated HR [23].