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Colorectal cancer and antiangiogenic therapy: What can be expected in clinical practice?

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Abstract

Angiogenesis is a strongly regulated process, which is dependent upon a complex interplay between inhibitory and stimulatory angiogenic factors. It is essential for tumor growth and metastasis: increased angiogenesis is correlated with poor prognosis in cancer patients. Many novel compounds that potently inhibit formation of neoplastic blood vessels have been recently developed. Major categories of angiogenesis antagonists include protease inhibitors, direct inhibitors of endothelial cell proliferation and migration, angiogenic growth factor suppressors, inhibitors of endothelial-specific integrin/survival signalling, copper chelators, and inhibitors with other specific mechanisms. There is increasing interest in developing angio-suppressive agents for colorectal cancer treatment. Some 20 direct and indirect antiangiogenesis drugs are currently being evaluated in clinical trials in colorectal cancer (CRC). Promising results have been reported. These include an increase

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in overall survival and reduction in the risk of death (Bevacizumab), reversal of cellular resistance (Cetuximab) and activity as second-line therapy in patients who have exhausted other available treatment options (Cetuximab, ABX-EGF, PTK-787, Gefitinib, Erlotinib). This review will outline the mechanisms of action of the principal antiangiogenic drugs, summarize the available data on the use of these new drugs in colorectal cancer, discuss their impact in clinical practice and offer a glimpse into how antiangiogenetic therapy will be integrated into the future care of patients with gastrointestinal cancers.

Keywords: Colorectal cancer; New regimens; Antiangiogenic therapy

1. Introduction

Tumor cells, like many other cell types, require vascularization to receive oxygen and nutrients and to dispose of catabolic products. While it has been known for a long time that new microvessel formation from endothelial cells (angiogenesis) accompanies tumor growth and favors metastatic dissemination, the identity and characteristics of the growth factors involved in this process have been recently defined in the past few years [1,2].

The list of growth factors involved in tumor angiogenesis has grown substantially and includes vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), Endostatin, platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF-alpha), tumor necrosis factor, and interleukin-8 (IL-8).

VEGF induces proliferation of vascular endothelial cells, promotes their survival in newly formed vessels, and increases microvascular permeability. The endogenous antiangiogenic factors Angiostatin and Endostatin, inhibit proliferation and migration of endothelial cells and induce apoptosis (cell death) in endothelial cells. After discovery of these mechanisms, it was only a matter of time before growth factors and receptors involved in angiogenesis would become targets for the development of novel antitumor therapies.

Angiogenesis inhibitors can be divided into two main categories of agents according to their mechanism of action [3]: those that act directly on microvascular endothelial cells recruited by the tumor, such as Endostatin, and those that target tumor growth factors (e.g., Bevacizumab, an antibody targeting VEGF) or tyrosine kinase inhibitors (TKIs) (e.g., Gefitinib, Erlotinib) (Table 1).

Advanced colorectal cancer (CRC) is a critical health concern, despite improvements during the last years. Overall survival is highly dependent upon the stage of disease at diagnosis. Estimated 5-year survival rates range from 85 to 90% for patients with stage I disease to <5% for patients with stage IV disease. Over 50% of patients with colorectal cancer presenting with metastatic or locally advanced disease experience local recurrence or develop distant metastases after potentially curative surgery. The most important treatment currently available for patients with stage IV disease is systemic chemotherapy. Although there have been recent advances in the field, with randomized trials confirming the activity of Irinotecan, Oxaliplatin and Capecitabine, median survival remains at only 15–18 months [4]. There is,

Table 1
Principal angiogenesis inhibitors in colorectal cancer: cellular targets and stage of clinical development

Agent/compound	Target	Mechanism	Clinical trial
Angiostatin	ATP synthase, Angiomotin, Annexin II	Inhibition of endothelial cell proliferation	Phase 1
Endostatin	Integrin alpha5-beta1	Inhibition of endothelial cell proliferation and migration	Phases 1 and 2
Vitaxin (humanized monoclonal antibody)	Integrin alpha 5-beta3	Inhibition of endothelial cell proliferation and migration	Phases 1 and 2
Canstatin	Integrin alpha5-beta3	Inhibition of endothelial cell proliferation and migration	Not yet
Bevacizumab (humanized monoclonal antibody)	VEGF	Inhibition of endothelial cell proliferation	Phases 2 and 3
Cetuximab (C-225), ABX-EGF	EGFR, VEGF, bFGF, TGF-alpha	Inhibition EGFR signalling and indirectly endothelial cell proliferation	Phases 2 and 3
EMD72000	EGFR, bFGF, TGF-alpha	It blocks EGFR and natural ligand binding; it abrogates receptor-mediated downstream signalling	Phase 1
AMG706	VEGF, PDGF, c-kit	Small molecule inhibitor of multiple kinases	Phase 1
NM-3 Isocoumarin	VEGF	Inhibition of endothelial cell proliferation	Phase 1
Gefitinib (ZD1839), Erlotinib (OSI-774), CI-1033	VEGF, bFGF, TGF-alpha	Inhibition of tyrosine kinase activation	Phases 1 and 2
SU-6668, PTK-787	VEGFR-1 and/or VEGFR-2	Inhibition of receptor phosphorylation	Phases 2 and 3
Combretastatins	Microtubules	Apoptosis of endothelial cells	Phase 1
2-Methoxyestradiol	Microtubules	Apoptosis of endothelial cells	Phase 1
Thalidomide and analogues	bFGF	Inhibition of endothelial cell proliferation	Phases 1 and 2

bFGF: basic fibroblast growth factor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor.