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Anti-angiogenic therapy, a new player in the field of sarcoma treatment

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Contents

Abstract

Sarcomas encompass a heterogeneous family of mesenchymal malignancies. In metastatic disease improvement in outcome has been limited and there is a clear need for the development of new therapies. One potential target is angiogenesis, already an accepted target for treatment of more prevalent cancers. Multiple (pre)clinical studies focused on the role of angiogenesis and anti-angiogenic treatment in sarcomas. However, getting significant results is complicated due to the relatively small number of patients and the broad range of sarcoma subtypes. Recently, pazopanib has been approved for the treatment of advanced soft tissue sarcoma patients, which is an important step forward and paves the way for the introduction of anti-angiogenic treatment in sarcomas. However, more studies are needed to understand the biological

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mechanisms by which patients respond to angiogenic inhibitors and to detect markers of response. This review covers the knowledge that has been gained on the role of angiogenesis and anti-angiogenic therapy in sarcomas.

Keywords: Angiogenesis; Sarcoma; GIST; Osteosarcoma; Chondrosarcoma; Soft tissue sarcoma; VEGF

1. Introduction

Microscopically small tumors can arise because of loss of control of cell proliferation. At a size of 1–2 mm diffusion becomes inadequate and proliferation is counterbalanced by necrosis. For further growth and invasive ability the tumor has to gain angiogenic properties by expressing several pro-angiogenic factors, *e.g.* vascular endothelial growth factor (VEGF), thereby changing the equilibrium between pro- and anti-angiogenic substances. This process is called the *angiogenic switch* and is triggered by oncogenic mutations, mechanic stress and hypoxia [1]. Hypoxia acts through the activity of hypoxia-inducible factor, HIF-1α, which forms an active transcription factor for proteins (among which are glucose receptors and VEGF) that allows the cells to adapt to a low pO_2 environment [2]. Endothelial cells and their precursors are stimulated to migrate to the extracellular matrix, proliferate and organize into new capillaries, a complex process that is still incompletely understood. Integrins, a family of transmembrane molecules which mediate numerous cell–cell and cell–matrix interactions such as cell adhesion, proliferation and apoptosis, are involved in this process. An important integrin is $\alpha_v\beta_3$, which is highly expressed in endothelial cells during angiogenesis. The VEGF family of tumor-secreted angiogenic factors (VEGF-A, VEGF-B, VEGF-C, and VEGF-D), and their receptors (VEGFR-1, -2, and -3 and Neuropilin), are only one group in a complex interaction of pro- and anti-angiogenic factors. They appear however to have a crucial role in tumor angiogenesis and enhancement of vascular permeability, which may in part be explained because VEGF acts as a mediator for indirect-acting angiogenic factors [3]. The different pathways in the cell combined make a complicated structure with numerous options for targeting.

In this review we describe the results of (pre)clinical studies concerning angiogenesis in sarcomas. Various anti-angiogenic compounds have been developed. These compounds, their targets and mechanism of action are listed in Table 1. The results of clinical trials with anti-angiogenic agents that included sarcoma patients are provided in Table 2.

Table 1
Mechanisms of action of the anti-angiogenic compounds discussed.

Compound	Manufacturer	Type	Target
Bevacizumab	Genentech	Humanized monoclonal antibody	VEGF-A
Vitaxin	Applied Molecular Evolution	Humanized monoclonal antibody	$\alpha\nu\beta3$
SU14813	Sugen	Tyrosine kinase inhibitor	VEGFR, PDGFR, KIT, FLT3
Orantinib	Sugen	Tyrosine kinase inhibitor	VEGFR, PDGFR, FGFR, KIT
Vatalanib	Novartis/Bayer	Tyrosine kinase inhibitor	VEGFR, PDGFR, KIT
Cediranib	AstraZeneca	Tyrosine kinase inhibitor	VEGFR, KIT
Sunitinib	Pfizer	Tyrosine kinase inhibitor	VEGFR, PDGFR, KIT, FLT3, RET, CSF-1
Sorafenib	Onyx/Bayer	Tyrosine kinase inhibitor	VEGFR-2, VEGFR-3, PDGFR, KIT, Raf/MEK/Erk pathway
Pazopanib	GlaxoSmithKline	Tyrosine kinase inhibitor	VEGFR, PDGFR, KIT
Motesanib	Amgen	Tyrosine kinase inhibitor	VEGFR, PDGFR, KIT
Semaxanib	Sugen	Tyrosine kinase inhibitor	VEGFR-2, KIT
Vandetanib	AstraZeneca	Tyrosine kinase inhibitor	VEGFR, EGFR, RET
Dasatinib	Bristol-Myers Squibb	Tyrosine kinase inhibitor	BCR/ABL, KIT, Src
Regorafenib	Bayer	Tyrosine kinase inhibitor	VEGFR, KIT, RET, PDGFR, FGFR, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, $BRAF^{V600E}$, SAPK2, PTK5, and Abl pathways.
ABT510	Abbott	Thrombospondin analog	VEGF, bFGF, HGF, IL8
TNP470	Tocris	Analog of Fumagillin	Methionine aminopeptidase type II (MetAP2)
Aflibercept (VEGF Trap)	Sanofi	Protein comprised of segments of the extracellular domains of human VEGFR1 and VEGFR2 fused to the Fc region of human IgG1. Functions as a soluble decoy receptor, binds to VEGFs thereby preventing VEGFs from binding to their cell receptors	VEGFR

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