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Review

Aflibercept a new target therapy in cancer treatment: a review

Vincenzo Ricci[a,*], Monica Ronzoni[a], Teresa Fabozzi[b]

[a] Oncology Department, San Raffaele Institute, 60, Olgettina St., 20132 Milan, Italy
[b] San Raffaele Institute, 60, Olgettina St., 20132 Milan, Italy

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ABSTRACT

Angiogenesis is the process through which new blood vessels are formed from pre-existing vessels and is essential for the growth of all solid tumors. Vascular endothelial growth factor (VEGF) is a regulator of angiogenesis, which is crucial for tumor growth and metastasis. Its inhibition with antiangiogenic drugs is thought to improve delivery of chemotherapy through vascular normalization and disruption of tumor vasculature. Aflibercept is a recombinant fusion protein of the VEGF receptor (VEGFR)1 and VEGFR2 extracellular domains that binds to VEGF-A, VEGF-B, placental growth factor (PlGF) 1 and 2. Aflibercept has demonstrated preclinical efficacy in different tumor types and exerts its antiangiogenic effects through regression of tumor vasculature, remolding of vasculature, and inhibition of new tumor vessel growth. This review examines the effects of aflibercept on tumor vasculature and on different types of solid tumors, and explores the preclinical and clinical benefits of inclusion aflibercept into anticancer treatment strategies.

1. Introduction

Angiogenesis is an important process of new blood vessel formation and is one of the cardinal processes leading to invasion and metastasis of solid tumors (Ferrara, 2004; Hicklin and Ellis, 2005). It was described by Folkman almost 40 years ago. He proposed that without angiogenesis tumor could reach a size of <3 mm and would then enter in a state of dormancy, but the release of certain signals by malignant cells could enable blood vessels formation. Such as angiogenic switch, in which the balance between pro-angiogenic and anti-angiogenic factors shifts in favour of pro-angiogenesis, is considered as one of the hallmarks of malignancy (Folkman, 1971).

In fact, this process is controlled by a complex signaling network that involves multiple interacting proangiogenic and antiangiogenic signals, including vascular endothelial growth factor (VEGF), angiopoietins and integrins. VEGF system is the predominant regulator of tumor angiogenesis. Its continued expression, along with the proposed genetic stability of VEGF and endothelial cells, makes direct and continuous targeting of VEGF an important antitumor strategy (Folkman et al., 2005; Mukhopadhyay and Datta, 2004; Wulff et al., 2002). Aflibercept is a soluble recombinant fusion protein designed to block the angiogenesis network binding to all isoforms of VEGF and to placental growth factor (Kim et al.,

Abbreviations: VEGF, vascular endothelial growth factor; PlGF, placental growth factor; VEGFR, vascular endothelial growth factor receptors; NRP, neuropilin receptor; Ang, angiopoietins; RTKs, receptor tyrosine kinases; DLL, delta-like ligand; PDGF, platelet derived growth factor; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor-β; vHL, von Hippel-Lindau syndrome; PI3K, phosphatidylinositol 3′ kinase; mCRC, metastatic colon-rectal cancer; RCC, renal cell carcinoma; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; HER2, human epidermal growth factor receptor-2.

* Corresponding author at: Department of Medical Oncology, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy. Fax: +39 02 26437603.

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2002a; Holash et al., 2002). It developed by fusing sections of second immunoglobulin (Ig) domain of VEGFR-1 and the third Ig domain of VEGFR-2 to the Fc portion of human IgG (Shibuya, 2010; Inai et al., 2004; Huang et al., 2003).

This review examines the effects of aflibercept on tumor vasculature, and how these translate into preclinical and clinical efficacy. It also examines the preclinical and clinical benefits of incorporating aflibercept into anticancer treatment strategies, including which agents can be combined with aflibercept.

2. Angiogenesis pathways, antiangiogenic agents and their effects on tumor vasculature

The diversity of pathways involved in angiogenesis offers numerous possible therapeutic targets. The VEGF family has been greatly implicated as a key regulator of tumor angiogenesis and is composed of 5 glicoproteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) (Ellis and Hicklin, 2008; Grothey and Galanis, 2009; Fischer et al., 2008).

These growth factors exert their biological effects through binding with three different VEGF receptors (VEGFRs) classified as: VEGFR-1, VEGFR-2, and VEGFR-3. The activities of these receptors can be enhanced by co-receptors neuropilin receptor (NRP)-1 and NRP-2. (Veikkola and Alitalo, 1999; Chu, 2009).

The VEGF pathways cross with a number of other signaling pathways involved in the coordination of tumor angiogenesis. The angiopoietins (Ang-1, Ang-2, and Ang-4) interact with the receptor tyrosine kinases (RTKs) with immunoglobulin-like and EGF-like domains Tie1 and Tie2 (tyrosine kinases inversely regulate embryonic angiogenesis). Both Ang-1 and Ang-2 have been associated with protumor and antitumor angiogenic effects. Ang-2, found on endothelial cells, is felt to destabilize vessels and amplify the activity of VEGF-A. Overexpression of Ang-2 and higher Ang-2:Ang-1 ratios were found to be correlated with poor prognosis in many cancers, including metastatic colon-rectal cancer (mCRC). Integrins expressed on varied cell surfaces also promote angiogenesis and interact with both the VEGF and Ang-Tie pathways (Huang et al., 2003; Qiao and Wong, 2009).

The Notch-signaling pathway consists of the ligands Jagged1, Jagged2, delta-like ligand (DLL) 1, DLL3, DLL4, and the Notch receptors, Notch1-4. DLL4 is upregulated by VEGF-A, and is felt to represent a negative feedback mechanism to angiogenesis under physiologic conditions. In tumor cells, however, the interaction between DLL4- expressing and Notch1-expressing cells has been observed as a component of angiogenesis. Notch-signalling pathway has been shown to play a critical role in multiple cancers, including CRC. Increased DLL4 expression was found preferentially in CRC endothelial cells and was associated with VEGF expression. Notch signaling has also been shown to promote angiogenesis via upregulation of VEGFR-3. This angiogenic activity proceeds independent of VEGF-A, VEGF-C, or VEGFR-2 (Qiao and Wong, 2009).

VEGF-A was the first member of the VEGF family to be identified and is identified as the most potent inducer and positive regulator of the normal and pathologic angiogenic cascade. It regulates blood vessel proliferation and vascular permeability, and its expression is associated with poor prognosis in a variety of human cancers (Shweiki et al., 1995). The biological effects of VEGF-A include endothelial cell proliferation, survival, migration, invasion, chemotaxis of bone marrow progenitors, vascular permeability, and vasodilation, which are mediated by its binding and activation of receptor tyrosine kinases VEGFR-1 and VEGFR-2 (Ellis and Hicklin, 2008). Although VEGF-A binds VEGFR-1 with approximately 10 times higher affinity than VEGFR-2, the higher kinase activity of VEGFR-2 makes it the most important effector of VEGF-A signaling (Shibuya, 2010; Shalaby et al., 1995).

VEGF-A is the best-characterized member of the VEGF family. However experimental and clinical evidence indicates that other VEGFs, such as VEGF-B and PlGF, play an important role in tumor biological processes and pathologic angiogenesis. VEGF-B shares close structural homology with VEGF-A; although these factors are coexpressed in many tissues, VEGF-B is more broadly expressed in skeletal muscle and the pancreas. VEGF-B binds VEGFR-1 and NRP1 and although still under investigation, it could play a role in tumorigenesis and angiogenesis (Olofsson et al., 1998).

Assumption is that both VEGF-B and VEGFR-1 are upregulated in a number of different tumor types in some cases, correlating with poor prognosis, metastasis, and relapse. VEGF-B has been shown to have pleiotropic effects on vascular cell adhesion, and although it seems to be dispensable for the growth of blood vessels, VEGF-B may play a role in the survival of preexisting blood vessels under pathologic conditions (Zhang et al., 2009). PlGF exists as at least 4 different isoforms originated by alternative splicing: PlGF-1, PlGF-2, PlGF-3, and PlGF-4. Similar to VEGF-B, PlGF is also homologous to VEGF-A and binds VEGFR- 1. PlGF-1 and PlGF-2 levels have been shown to be elevated in human colorectal tumors. In addition there is evidence that PlGF increase the response to VEGF-A by signaling through VEGFR-1, and this signaling stimulates the recruitment of bone marrow-derived macrophages to the tumor site, where they release angiogenic factors.

VEGF release is induced by metabolic stress (hypoxia, pH reduction), inflammation, platelet derived growth factor (PDGF), tumor necrosis factor α (TNF-α), transforming growth factor-β (TGF-β) and by inactivation of the von Hippel–Lindau sindrome (vHL) tumor suppressor gene. Ligand–receptor interaction induces the activation of VEGFRs tyrosine kinase domain and consequently of intracellular signal transduction pathways involved in regulation of cellular proliferation and survival, such as the Raf/ mitogen-activated protein kinase — extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) [Raf/Mek/Erk] and the phosphatidylinositol 3′ kinase (PI3K)/protein kinase B (Akt) [PI3K/Akt] pathways (Neufeld et al., 1999). Due to the central role of the VEGF family in angiogenesis, and the increased VEGF expression in many tumor types, this family of growth factors has become an important therapeutic target (Yang et al., 2003; Sawano et al., 1996; Escudero-Esparza et al., 2009).

The drugs used to target VEGF do not need to penetrate tumor tissue to inhibit angiogenesis because VEGF circulates in the blood and acts directly on vascular endothelial cells. The effect of VEGF can be blocked in two ways: by using monoclonal antibodies against VEGF or by using the inhibitors of the tyrosine kinase activity of the VEGF receptors.

However, angiogenesis inhibitors are subject to the same limitation of other antineoplastic drugs of the eventual observed resistance that results after prolonged exposure to these agents. Some evidence show that tumors start secreting their own growth factors, which changes their dependence on the stromal factors. Alternate growth stimulators (PlGF, bFGF, PDGF) have been reported in anti-VEGF-therapy resistant patients to develop strategies to overcome resistance to angiogenesis inhibitors, one must first be able to properly recognize the complexity of defining drug resistance in the clinic (Kerbel, 2008).

Much investigation has been carried out by various laboratories to better define preclinically the resistance pathways that arise in tumor cells that allow them to overcome angiogenesis targeting strategies. One such example are integrins, which are major mediators in the interactions between cancer cells and the tumor microenvironment. Specifically, β1 integrin signaling in tumor cells has been shown to promote resistance to radiotherapy and chemotherapy, and acts through downstream signaling pathways, such as FAK, ERK/MAP kinase, Src, Akt and Ras. Microarray gene expression analyses and immunohistochemistry have demon-