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Cardiac and vascular toxicities of angiogenesis inhibitors: The other side of the coin

Raafat S. Alameddine [a], Ahmad Sharif Yakan [b], Hadi Skouri [c], Deborah Mukherji [a], Sally Temraz [a], Ali Shamseddine [a,*]

[a] *Division of Hematology and Oncology, American University of Beirut, Beirut, Lebanon*
[b] *Division of Cardiology, University of Rostock, Rostock, Germany*
[c] *Division of Cardiology, American University of Beirut, Beirut, Lebanon*

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Contents

Summary

Angiogenesis is one of the best-described tumor hallmarks. Targeting angiogenesis is becoming a successful strategy to suppress cancer growth. Vascular endothelial growth factor (VEGF), the fulcrum of angiogenesis, contributes to vascular and cardiac homeostasis.

* Corresponding author. Tel.: +961 1350000.
E-mail address: as04@aub.edu.lb (A. Shamseddine).

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Angiogenesis inhibitors classically associated with vascular side effects are increasingly recognized for cardiac adverse effects as reflected by several meta-analyses. A global approach to these findings is a pressing need, and future strategies involving collaboration among different medical specialties are highly encouraged.

Keywords: Angiogenesis; Cardiac adverse effect; Vascular adverse effect; Pathogenesis

1. Angiogenesis in cancer

Angiogenesis underlies a wide range of physiological processes including embryogenesis, the female reproductive system and wound healing [1–5]. Angiogenesis depends on a complex network of ligands, receptors and intracellular signaling cascades [4]. Delicate balance between activators and suppressors of angiogenesis is crucial for proper neovascularization. Disruption of the physiological equilibrium translates into different pathological states including preeclampsia, diabetic retinopathy and rheumatoid arthritis [6–8]. In cancer, angiogenesis is considered as one of the hallmarks of malignancy [9]. Besides contributing to tumor growth and metastasis, angiogenesis is intimately tied with other neoplastic traits [10]. Vascular endothelial growth factor (VEGF) represents an attractive therapeutic target in many areas of oncology [11] and targeting angiogenesis has become one of the most promising strategies in cancer therapy [12]. Targeting angiogenesis is associated with a disruption in the equilibrium state achieved by balance between pro and anti-angiogenic factors. The cardiovascular system is deeply affected by the alteration in the angiogenic activity. This review provides a conceptual framework for cardiac and vascular toxicities of angiogenesis inhibitors based on preclinical and clinical data, and concludes with a set of practical steps for research and daily practice.

2. The angiogenesis network

The VEGF family is composed of 6 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and VEGF-F, each with a unique pattern of receptor affinity (Fig. 1). In addition, Placenta growth factor (PlGF), tumor necrosis factor-α (TNF-α), transforming growth factors (TGF), platelet-derived growth factor (PDGF) and fibroblast growth factors (FGF) contribute to the angiogenic mesh [13–15].

VEGF is key for the orchestration of angiogenic signaling for early development and organogenesis [16–18]. VEGF knock-out or inhibition were both lethal for murine embryos [19]. VEGF is also present at lower yet detectable levels in normal adult tissues [20,21]. VEGF expression is maintained in adulthood. The highest levels of VEGF expression in normal tissues are found in the heart, lungs, kidneys, and adrenal glands. In contrast, VEGF is expressed minimally in the liver, spleen and gastric mucosa [20,21]. The differential expression of VEGF transcripts highlights its role in vascular homeostasis in addition to angiogenesis and neovascularization.

VEGF-A binds to two highly related receptor tyrosine kinases: vascular endothelial growth factor receptor 1 (VEGF-R1) and vascular endothelial growth factor receptor 2 VEGF-R2 [17,22,23]. The exact intracellular pathway conveyed by VEGF-R1 signaling remains to be elucidated [17]. VEGF-R1 functions in the vascular endothelium include the release of growth factors, induction of matrix metalloproteinase 9 (MMP-9), hematopoiesis and neutrophil chemotaxis. VEGFR2 is the major mediator of angiogenic and permeability enhancing effects of VEGF-A and mediates release of nitric oxide (NO) and prostacyclin (PGI2) from endothelial cells.

3. Angiogenesis in vascular physiology and disease

3.1. Endothelial dysfunction

Normal expression of VEGF in tissues maintains density of existing endothelial cells and basal permeability of the normal microcirculation [20,21]. Blockade of VEGF receptors in mice results in a dramatic capillary regression in a variety of adult tissues [24,25]. VEGF-A stimulates the growth of vascular endothelial cells derived from arteries, veins, and lymphatics [26,27]. Binding of VEGF to its receptors on the endothelial cells conveys survival messages and prevents apoptosis. Binding of VEGF-A to VEGFR-2 is thought to activate the phosphatidylinositol 3′-kinase (PI3K) pathway and translates into increased expression of anti-apoptotic factors such as B-cell lymphoma 2 (BCL-2), and Survivin [19,28–30]. Inhibition of VEGF causes regression in capillary density in a process known as rarefaction as demonstrated in the mucosa of patients receiving treatment with VEGF-A blockade by Bevacizumab [31]. Interestingly, inhibition of VEGF results in regression of neonatal but not adult vasculature suggesting differential role in different development stages [32].

3.2. Thrombosis

VEGF is fundamental in maintaining endothelial cell homeostasis especially in response to stress and/or injury [33,34]. Binding of VEGF-A to VEGF-R2 on the surface of endothelial cells, leads to the release of nitric oxide (NO) and prostacyclin (PGI2) with subsequent relaxation