Cardiovascular Effects of Anti-angiogenic Drugs

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13.1 Introduction

Cancer treatment is the cause of an emerging chronic cardiovascular health problem in cancer survivors. Data show that more than 1.5 million people are diagnosed with a malignancy every year in the USA [1, 2], and in 2016, the American Cancer Society reported that there were 15.5 million cancer survivors in the country [1]. The 5-year survival rate for patients treated for cancer is currently 67% [1], but approximately 75% of these cancer survivors have some form of chronic health problems, of which cardiovascular diseases are the leading cause of morbidity and mortality [1]. The risk of cardiovascular disease is 8 times higher in cancer survivors than in the general population, and the relative risks of coronary artery disease and heart failure in cancer survivors are 10 times and 15 times higher, respectively, than in their siblings without cancer [1, 2].

There is a wide range of cardiovascular toxicities associated with anti-cancer therapy. Traditional chemotherapeutics, such as the anthracyclines, have been associated with severe cardiotoxicity, requiring strict control of the dose for a drug like doxorubicin [3]. With the emergence of many novel anti-cancer drugs, new forms of vascular toxicity, including systemic and pulmonary hypertension, stroke, acute coronary syndromes, arterial and arteriolar stenosis, and thrombosis, have been reported [4]. Due to an extensive drug discovery program by pharmaceutical and biotech companies, there has been an explosion of novel anti-cancer agents on the market (Table 13.1). In particular, monoclonal antibodies, VEGF-receptor fusion

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Table 13.1 Major classes of anti-cancer drugs

Antimetabolites
Alkylating agents
Vinca alkaloids
Proteasome inhibitors
Monoclonal antibodies
VEGF receptor fusion molecules
Antimicrotubule agents
Tyrosine kinase inhibitors

Table 13.2 Tyrosine kinase inhibitors

Sorafenib
Sunitinib
Pazopanib
Axitinib
Regorafenib
Cabozantinib
Vandetanib
Lenvatinib
Nilotinib
Ponatinib
Dasatinib

molecules, and tyrosine kinase inhibitors (TKIs; Table 13.2) have been brought to the market rapidly without thorough investigation of their potential cardiovascular side effects.

13.2 Mechanisms of Angiogenesis

A common feature of the three recently introduced classes of anti-cancer drugs (Table 13.2) is that they inhibit the action of vascular growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) [5]. These growth factors stimulate, via the enzyme tyrosine kinase, a range of signal transduction molecules that cause angiogenesis of the tumor, invasion of tissues, and metastasis. The role of angiogenesis in cancer progression and of angiogenesis inhibition as a form of cancer treatment was introduced several decades ago by Judah Folkman, when he observed an association between solid tumor growth and vascular supply [6, 7]. He showed that a soluble factor isolated from tumor tissue could promote neovascularization of tumors in vivo. A few years later, this substance was identified and sequenced as the vascular endothelial growth factor (VEGF) [8]. In the decades following these early observations, our understanding of the process of angiogenesis has increased substantially, and the reader is referred to recent review articles for more detailed information [9, 10].

The VEGF signaling pathway plays a central role in the development of anti-angiogenic drugs. VEGF is one of the five members of a family of structurally

related proteins that are involved in the regulation of vascular endothelium [11]. The VEGF gene undergoes alternative splicing to form these multiple isoforms. The VEGF gene is upregulated by hypoxia, reactive oxygen species, inflammatory cytokines, and other growth factors [12]. VEGF binds three tyrosine kinase receptors leading to a tyrosine kinase signaling cascade that stimulates production of factors that induce vasodilation, cell proliferation migration, and differentiation into mature blood vessels [12, 13]. Major signaling pathways include phosphoinositide 3-kinase/Akt/protein kinase B-mammalian target of rapamycin and activation of endothelial nitric oxide (NO) synthase and inducible NO synthase, leading to downstream release of potent vasodilators, including NO and prostacyclin [12, 13]. Besides promoting angiogenesis, VEGF also increases vascular permeability and is required for the maintenance of a differentiated EC phenotype and EC survival [13]. It thus has many physiological actions, including angiogenesis during embryogenesis, wound healing, and menstruation [12]. In preeclampsia, a placenta-derived tyrosine kinase, a splice variant of the VEGF gene, is markedly increased, thereby contributing to the pathophysiology of this condition, characterized by hypertension, proteinuria, and edema [13, 14].

13.3 Anti-angiogenic Drugs in Cancer Treatment

The VEGF signaling pathway (VSP) has been a primary target for the development of anti-angiogenic drugs. Table 13.2 summarized the major anti-angiogenic drugs from the tyrosine kinase inhibitors group. More than ten of the representatives of this class have been or are currently investigated for their anti-cancer potential. All these agents are small molecule multiple TKIs with varying specificities for VEGF receptor subtypes. Because the kinase domains in the VEGF receptors share structural similarity with the kinase domains in other signaling receptors, these TKIs target multiple pathways [11]. These drugs have been approved for the treatment of different forms of cancer, including gastrointestinal stromal tumors, advanced renal cell carcinoma, advanced pancreatic neuroendocrine tumors, advanced hepatocellular carcinoma, metastatic medullary thyroid cancer, and metastatic colorectal cancer. It is beyond the scope of this chapter to critically review the effects of these drugs in each of these forms of cancer. The reader is referred to recent specialized reviews for this purpose [11, 15–17].

Despite the recent explosion of VSP inhibitors, the benefits of these agents have thus far been modest [11]. There is still a lack of understanding how different cancers become vascularized and how they evade the effects of anti-angiogenic therapy by building up resistance towards VEGF-targeted therapy. In addition, incomplete knowledge on duration and scheduling of therapy as well as toxicities hampers the optimal therapy with anti-angiogenic drugs. The use of predictive biomarkers may be a way to closely monitor their therapeutic efficacy [15].

13.4 Adverse Cardiovascular Effects of Anti-angiogenic Drugs

Hypertension is the most common cardiovascular effect of VSP inhibitors, and its underlying mechanisms will be dealt with in the next section of this chapter. A second important potential toxic target of VSP inhibitors is left ventricular dysfunction and cardiomyopathy. Although it is difficult to judge in cancer patients with complex clinical condition and multiple chemotherapeutic interventions to what degree VSP inhibitors specifically cause left ventricular dysfunction, both retrospective observational data from individual trials with VSP inhibitors and meta-analyses suggest that up to 30% of patients had an absolute decrease in ejection fraction [11, 18]. Similar analyses suggest a significantly increased incidence of cardiomyopathy [11, 18]. One of the most logical explanations for VSP inhibitor-induced cardiomyopathy is a decreased capillary density (rarefaction) in the heart, causing hypoxia and cardiac dysfunction [19].

A further potential cardiovascular toxicity of VSP inhibitors is arterial and venous thromboembolism. Numerous studies have suggested that the incidence of thromboembolic events is increased in patients treated with VSP inhibitors [11, 18]. Meta-analyses have shown an incidence of thromboembolic events in cancer patients treated with VSP inhibitors of around 12%, depending on the type of cancer treated [20]. Mechanisms underlying the thromboembolic events in VSP inhibitor-treated patients include alterations in endothelial cell function and expression of various factors involved in hemostasis and thrombolysis as well as immune complex-mediated platelet activation [11, 18].

13.5 Angiogenesis Inhibition-Related Hypertension: Incidence

Hypertension is a common side effect of cancer treatment with VSP inhibitors. The reported incidence of hypertension shows a wide range, depending on the agents used, their dosing schedule, the type of cancer treated, and the diagnostic criteria for hypertension classification. Several recent review articles summarize these different results [11, 12, 21–23]. A particularly important source of difference in incidence data is the level of blood pressure regarded as hypertensive and the method by which blood pressure is assessed. In view of the recent controversies between hypertension guidelines in different parts of the world as well as the classification systems used by cancer expert organizations to assess chemotherapeutic toxicities, it is difficult to give exact incidence data [12, 21].

Almost 100% of patients treated with VSP inhibitors have an absolute increase in blood pressure, with a subset developing chronic hypertension [12]. Data used from meta-analyses indicate that the overall hypertension incidence during VSP inhibitor treatment ranges from 20% to 90% [12]. The blood pressure increase induced by VSP inhibitors occurs rapidly within hours to days after start of treatment. Ambulatory blood pressure monitoring demonstrated that blood pressure

increases over the first 24 h after start of the therapy, with sustained blood pressure increase after 1 week [12, 24].

Hypertension can rapidly lead to levels >150/100 mm Hg which may require adjustment of VSP inhibitors dosing or start antihypertensive treatment. For a detailed overview of the management of VSP inhibitor-induced hypertension, the reader is referred to a recent excellent review article [23].

13.6 Mechanisms of VSP Inhibition-Related Hypertension

Table 13.3 summarizes the most important mechanisms that have been implicated in VSP inhibition-related hypertension. The first suggestion that angiogenesis may cause hypertension stems from the 1990s—before VSP inhibitors were on the market—in several papers reviewing the role of microvascular density in the pathogenesis of hypertension [25, 26]. There is convincing evidence in the meantime that small arteriolar and capillary rarefaction are major hallmarks of hypertension [27, 28]. Such evidence was obtained in various animal models for hypertension but was more difficult to obtain in humans because of lack of methodologies to assess human microcirculation. Recent technological innovations, particularly in the area of studies of the retina, have confirmed the important role of structural microvascular changes in the development and maintenance of hypertension in humans [29, 30]. In several clinical studies, capillary rarefaction has been shown in response to anti-angiogenic agents [23, 31–33].

Other potential mechanisms of VSP inhibition-related hypertension focus on changes in endothelial cell function. Inhibition of the nitric oxide signaling pathway has been raised on the basis of experimental animal models, but clinical studies have not been conclusive thus far [13, 22]. An interesting alternative endothelium-related mechanism was proposed by Danser and co-workers in a series of both clinical and experimental studies, measuring endothelin metabolism [13, 34]. In these studies, they found that antiangiogenic treatment increases endothelin-1 levels. Besides increased endothelin-1 levels, VEGF inhibition is associated with an increased vasoconstrictor response to endothelin-1. These studies suggest a possible therapeutic solution to VSP inhibition-related hypertension by means of the use of endothelin receptor blockers.

Less well-established potential mechanisms of VSP inhibition-related hypertension involve increased production of reactive oxidative stress molecules and arterial stiffening [12, 22]. Further research is needed to confirm the role of these latter mechanisms in the etiology and treatment of VSP inhibition-related hypertension.

Table 13.3 Potential mechanisms of VSP inhibitor-induced hypertension

Microvascular rarefaction
Reduced NO production
Reduced prostacyclin production
Increased generation of endothelin
Increased production reactive oxygen species
Renal dysfunction
Increased arterial stiffness

13.7 Conclusion

Angiogenesis is a fundamental mechanism in dynamics of the structure of the microcirculation. It contributes both to the maintenance of an optimal perfusion of tissues as to the spread and growth of tumors. Thus, anti-angiogenic drugs can be expected to be double-edged swords, inhibiting tumor growth on the one hand but interfering with cardiovascular control of blood pressure and tissue perfusion on the other hand. In this respect, hypertension is not an unexpected frequent consequence of anti-angiogenic therapy.

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