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Cardiovascular implications of anti-angiogenic therapeutic agents in cancer patients

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The advent of anti-angiogenic agents has impacted cancer therapeutic strategies. Anti-angiogenic agents along with standard cancer therapies have improved the survival and the prognosis of cancer patients in select diseases [1]. Various anti-angiogenic agents that target the vascular endothelium growth factor (VEGF) pathway are currently used in cancer therapy including intravenous and oral formulations. Bevacizumab and ramucirumab are examples of the former, and tyrosine kinase inhibitors such as sunitinib, sorafenib, cabozantinib, lenvatinib, pazopanib, and axitinib are examples of the latter [2]. The use of anti-angiogenic agents is approved for the treatment of various cancers including metastatic liver, kidney, colorectal, ovarian, gastric, thyroid, and soft tissue cancers [3,4]. Through the disruption of angiogenesis, the process of formation of new microvasculature from the pre-existing vessels, anti-angiogenic agents help impede tumor progression by altering tumor growth and metastasis [5]. Inhibition of angiogenesis halts the vascular endothelium growth factor signaling pathways resulting in the suppression of tumor neovascularization [6].

Anti-angiogenic agents are relatively well tolerated short of few adverse events one need to care for including but not limited to bleeding potential and hypertension [7,8]. Theoretically, it is thought that the probability of anti-angiogenic agents to cause side effects is low because angiogenesis is the central process for tumor progression and has a limited role in healthy cells [9]. However, the specificity of VEGF inhibitors is not absolute; they may have off-target effects [10]. With continued improved overall survival, long-term adverse effects have emerged and continue to be better understood [11]. Studies have shown that the anti-angiogenic agents can directly affect cardiovascular and endothelial cells [12]. Among the long-term adverse effects is therapy-induced premature aging of cardiovascular and endothelial cells [13].

One of the hallmarks of cellular aging is cellular senescence [14]. Once cells become senescent, alterations in the production of inflammatory cytokines and chemokines and changes within the cell chromatin occur [15]. These changes eventually lead to accelerated aging and premature frailty [11]. Cellular senescence can be involved in normal physiological roles in embryonic development, wound healing, and suppression of tumor growth [15]. However, persistence of senescence disrupts homeostasis and contributes to aging and the development of several diseases. Cardiovascular aging because of vascular and endothelial senescence is an entity that has been described [16]. Endothelial cells are at a risk of increased aging due to cancer therapy-induced toxicity [11]. Senescent endothelial cells demonstrate alterations in cellular function that can induce endothelial dysfunction and vascular impairment [11]. Early-senescence of cardiovascular and endothelial cells can lead to multiple cardiovascular complications especially among cancer survivors as they live longer. Vascular and endothelial senescence has been identified as a significant contributor to multiple cardiovascular diseases including atherosclerosis, hypertension, and stroke [17].

Although several mechanisms have been proposed to explain the molecular mechanisms of cancer therapy-induced complications, therapy-induced premature aging mediating the cardiovascular complications has emerged [11]. Angiogenesis inhibitors through myocardial capillary rarefaction, coupled with induction of hypoxia and hypoxia-inducible genes, and the resulting cardiac dysfunction, as well as vascular constriction, are among the recently described mechanisms by Kreidieh and McQuade (2024) [18]. Cardiovascular diseases and cancer possess various similarities and possible interactions, including several similar risk factors, such as obesity and diabetes mellitus [19]. The question regarding the role of genetic susceptibility has been proposed. Tet methylcytosine dioxygenase 2 (TET2), which is a common gene identified as an acquired mutation in individuals without hematological malignancies, has been shown to be the most common mutated gene associated with increased incidence and mortality due to cardiovascular disease [20].

As we navigate the implications of anti-angiogenic agents on the cardiovascular system, collaboration among oncologists, cardiologist and other healthcare professionals is of utmost importance. Studies have shown that the risk starts within the first decade of cancer therapy and is associated with the nature of the cancer, treatment, common risk factors, inflammation, and genetic predisposition [21]. Close monitoring of

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blood pressure and cardiac function are essential parameters that need to be followed [18]. Risk stratification strategies tailored to individual patient profiles can help identify patients at increased risk of cardiovascular adverse events. Early detection enables timely interventions and ultimately improved outcomes. Ensuring that therapeutic benefits are maximized while minimizing the cardiovascular burden on patients is essential as the balance among therapeutic efficacy of these agents and their subsequent cardiovascular safety is delicate. A multidisciplinary approach and a holistic perspective fostering collaboration among various medical specialties can help mitigate the cardiovascular risks associated with antiangiogenic agents and ensure safer treatment pathway for cancer patients.

In summary, the care for cancer patients extends beyond the management of the disease itself and entails dedication to preserving their cardiovascular and overall well-being. In addition to closely monitoring and addressing the cancer, healthcare professionals must remain vigilant in detecting and managing potential cardiovascular toxicities including atherosclerosis, hypertension, and stroke that are not always apparent until later.

CRediT authorship contribution statement

Layal Al Mahmasani: Conceptualization, Writing – original draft, Writing – review & editing. **Ghassan K. Abou-Alfa:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

LA has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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