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Review

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Mechanism and Management of Cancer Chemotherapy-Induced Atherosclerosis

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The advent of new chemotherapeutic and immunotherapeutic treatments has markedly improved outcomes in patients with cancer. However, increasing numbers of elderly patients with cancer and prolonged periods of treatment have made the management of cardiovascular complications and treatment-induced cardiotoxicity an important concern, and onco-cardiology has received increasing attention. The number of patients with cardiotoxicity, particularly atherosclerotic lesions, and the usage of angiogenesis inhibitors have increased, making the involvement of onco-cardiologists essential for effective disease management. A paradigm shift in immunotherapy was caused by the development of immune checkpoint inhibitors. Because vascular endothelial growth factors (VEGF) in the cancer microenvironment and cancer immune function are interrelated angiogenesis inhibitors will most likely play an increasingly important role in combined immunotherapy. To ensure the optimal long-term diagnosis and long-term treatment of cancer and the effective management of treatment-related atherosclerotic diseases, the long-term continuous participation of onco-cardiologists is essential.

Key words: **Cancer, Cardiotoxicity, Vascular endothelial growth factors, Immune checkpoint inhibitors, Atherosclerosis**

Introduction

In Japan, 1 in 2 individuals will have cancer during their lifetime. Progress in cancer therapy, particularly the development of chemotherapy and immunotherapy, has markedly improved outcomes in patients with cancer. On the other hand, Westernization of lifestyle and rapid aging of population have led to increasing numbers of patients with cancer and cardiovascular disease. The management of cardiotoxicity caused by new cancer treatments has become an important problem. Attention has focused on atherosclerotic disease occurring with the westernization of lifestyle, the aging of patients with cancer, and as cardiotoxicity associated with the prolonged use of anticancer therapy[1, 2]. Together with oncologists, onco-cardiologists, who actively participate in the diagnosis and treatment of both cancer and cardiovascular disease, aggressively contribute to the diagnosis and treatment of cardiotoxicity. Thereby, various cancer-specific and cancer-treatment-related problems are being solved[3]. In this paper, we outline the mechanism and management of atherosclerosis induced mainly by angiogenesis inhibitors, one of the most important factors, in patients with cancer treatment-related atherosclerosis.

1. Significance and Role of Angiogenesis Inhibitors in Patients with Cancer

Since Folkmann[4] reported the relation between angiogenesis and cancer cell proliferation, attention has focused on intracellular signaling pathways involved in angiogenesis as an important target of molecular-targeted drugs in cancer therapy. The roles and clinical significance of angiogenic factors, consisting mainly of vascular endothelial growth factors (VEGF) and VEGF receptors, have been elucidated. The main site of action of angiogenic factors is the vascular endothelium. Angio-

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genic factors act to induce endothelium-dependent vascular relaxation to maintain blood flow and promote angiogenesis. Mobilization of circulating endothelial progenitor cells from bone marrow is induced to promote angiogenesis[5]. In healthy adults, VEGF plays an important role in wound healing and the repair of vascular endothelial injury by promoting the production of nitric oxide (NO) and prostacyclin (PGI_2) in vascular endothelial cells to maintain normal blood flow. In pathological environments such as ischemic heart disease, VEGF secretion is stimulated by hypoxia-inducible factors (HIFs) associated with tissue ischemia, promoting compensatory angiogenesis. In the microenvironment of cancer, VEGF produced by cancer cells induces angiogenesis and proliferation required for the extension of cancer. In addition, VEGF plays important roles in the proliferation and metastasis of tumor tissue[6, 7]. In fact, VEGF is expressed in many types of cancers, including colorectal cancer, liver cancer, lung cancer, thyroid cancer, breast cancer, gastrointestinal cancer, renal cancer, bladder cancer, ovarian cancer, cervical cancer, angiosarcoma, germ cell tumors, and intracranial tumors. Angiogenesis inhibitors that target angiogenic factors were therefore developed for cancer therapy[8]. In 2004, bevacizumab, a representative anti-angiogenic agent, was developed as an anti-VEGF human monoclonal antibody. Its indications include colorectal cancer and have been expanded to include non−small-cell lung cancer, breast cancer, malignant glioma, ovarian cancer, and uterine cancer. Bevacizumab has been given to many patients with cancer and been reported to be effective[9].

2. Anti-Angiogenetic Agents and Drug-Induced Hypertension

Because angiogenesis inhibitors do not directly target cancer cells, these agents were initially suspected to be highly effective with few adverse reactions at the time of initial development. However, cardiotoxicity such as hypertension, thromboembolism, heart failure, and ischemic heart disease was reported in patients who received angiogenesis inhibitors. The incidence of hypertension was particularly high, and such cardiotoxicity required appropriate management. The incidences of hypertension caused by representative angiogenesis inhibitors are shown in **Table 1**[1, 10-13]. The times and the incidences of elevated blood pressure differed considerably according to the angiogenesis inhibitor being received.

A total of 197 patients with cancer who received bevacizumab in our hospital were studied retrospectively. The time of initiating treatment with the antihypertensive drugs and the time of onset of proteinuria were investigated. Grade 2 or higher hypertension developed in 38.6% of the patients who received bevacizumab, and antihypertensive drugs were required to control blood pressure. Proteinuria was positive in 41.6% of the patients. The times of elevated blood pressure varied from the day after starting treatment to within 1 week after starting treatment in some patients. In other patients, blood pressure rose after 4 or more weeks, and treatment was required. These various periods suggested that the mechanisms of blood pressure elevation varied considerably. As the dose of bevacizumab increased, increasing numbers of patients had elevated blood pressure and proteinuria, indicating that cardiotoxicity was dose-dependent[14].

Table 1. Incidence of hypertension after treatment with representative anti-angiogenetic agents.

Agents	Hypertension (%)
Monoclonal antibody-based tyrosine kinase inhibitors	
bevacizumab	23.6
ado-trastuzumab emtansine	5.1
Small molecular tyrosine kinase inhibitors	
sorafenib	15.3
sunitinib	21.6
axitinib	40.1
regorafenib	44.4
lenvatinib	67.8
pasopanib	42.0
vandetanib	24.2
mTOR (mammalian target of rapamycin) inhibitors	
everolimus	4-13
temsirolimus	7

Quoted from the following articles:
(01) Yeh ET, et al, JACC 2009; 53: 2231-2247.
(10) Zamorano Jl, et al, Eur Heart J.2016; 37 (36): 2768-2801.
(11) Moudgil R, et al. Can J Cardiol 2016; 32: 863-870.
(12) Wang Z, et al. Eur J Clin Pharmacol 2014; 70: 225-231
(13) Schlumberger M, et al. N Engl J Med 2015; 372: 621-630.

The main site of action of angiogenesis inhibitors is the vascular endothelium. Angiogenesis inhibitors are thought to act primarily on microvessels 150-200 μm in diameter. The mechanism by which angiogenesis inhibitors are thought to act on elevated blood pressure is shown in **Fig. 1**. Treatment with angiogenesis inhibitors causes vasoconstriction associated with decreases in vasodilators such as NO and PGI_2, resulting in vasoconstriction (vasoconstriction). In addition, vascular smooth muscle cell proliferation, platelet aggregation, thrombosis, and leukocyte adsorption to the vascular endothelium occur, promoting vascular endothelial dysfunction and the formation of plaque. On the other hand, vascular endothelial dysfunction and hypoxia promote the production of endothelin-1 (ET-1), causing vaso-

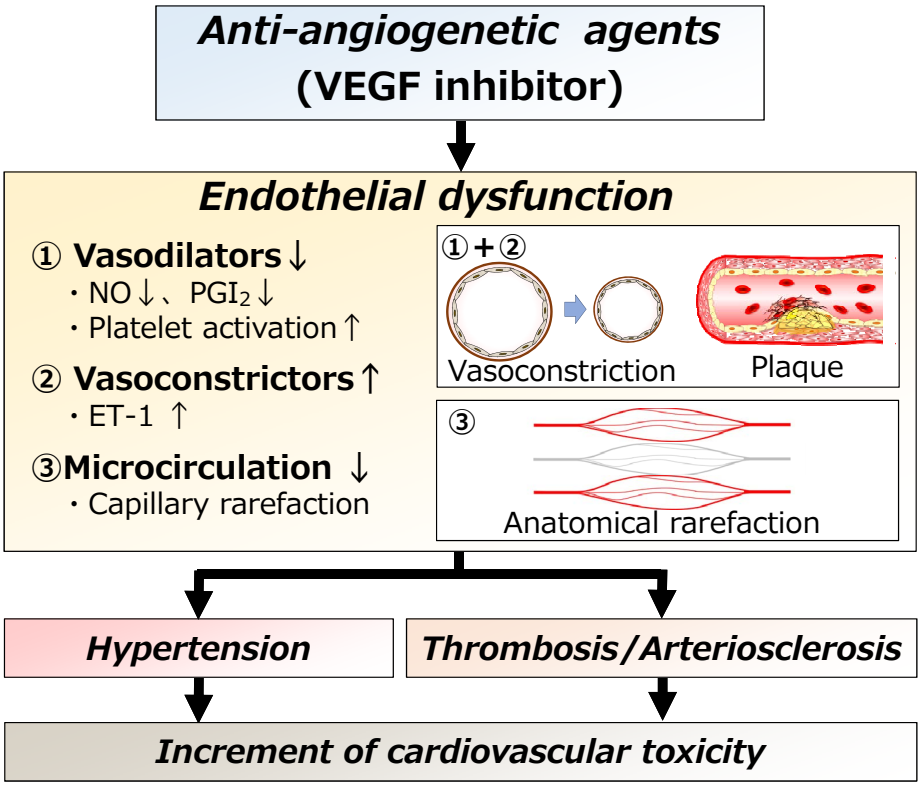

Fig. 1. Mechanism of cardiotoxicity associated with anti-angiogenetic agents (VEGF inhibitors).

① Decrease in vasodilator factors: NO and PGI_2, which are maintained by VEGF, are disturbed, resulting in vasospasm (vasoconstriction). In addition, platelet activity increases, leading to the formation of plaque (plaque). ② Increase in vasoconstrictors: ET-1 is increased by vascular endothelial dysfunction. ③ Microangiopathy: Microangiopathy occurs in association with a decrease in the peripheral vascular bed and microthrombus formation, resulting in capillary rarefaction and increased peripheral vascular resistance. This change becomes irreversible (anatomical rarefaction).

Quoted from the following articles:

(06) Chen, HX. and Cleck, JN. Nat Rev Clin Oncol 2009; 6: 465-477.
(07) Cameron AC et al., Can J Cardiol 2016; 32: 852-862.
(15) Zhu X et al. Am J Kidney Dis. 2007; 49: 186-193.
(16) Kappers MH et al., J Hypertens. 2009; 27: 2297-2309.
(17) Izzedine H et al. Ann Oncol. 2009; 20: 807-815.
(18) Vaklavas C et al. The Oncologist. 2010; 15: 1230-141.
(19) Kappers MH et al., Hypertension. 2010 Oct; 56(4): 675-681.
(20) de Jesus-Gonzalez N et al. Hypertension. 2012; 60: 607-615

constriction. Continuous treatment with angiogenesis inhibitors promotes a reduction in the peripheral arteriolar bed and capillary rarefaction associated with microthrombus formation, leading to microangiopathy (anatomical rarefaction). Consequently, hypertension and thromboembolism associated with atherosclerosis are induced, leading to drug-induced atherosclerosis[6, 7, 15-19].

The time of elevated blood pressure differs according to the action of VEGF inhibitors, as shown in Fig. 2. Immediately after the start of treatment, the functions of NO and PGI_2 are disturbed, and functional rarefaction due to vasoconstriction mainly occurs, resulting in reversible elevation of blood pressure. Continuous treatment with VEGF inhibitors results in a reduction in capillary rarefaction, and elevation of blood pressure in the chronic phase is attributed to anatomical rarefaction. Long-term treatment with angiogenesis inhibitors for more than several years has been reported to cause aortic dissection. Adequate caution should thus be exercised with respect to cardiotoxicity affecting medium and large blood vessels[20-22].

3. Multi-Targeted Tyrosine Kinase Inhibitors (TKIs) and Atherosclerotic Disease

Angiogenesis-related factors are known to include various factors besides VEGF, such as platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF),

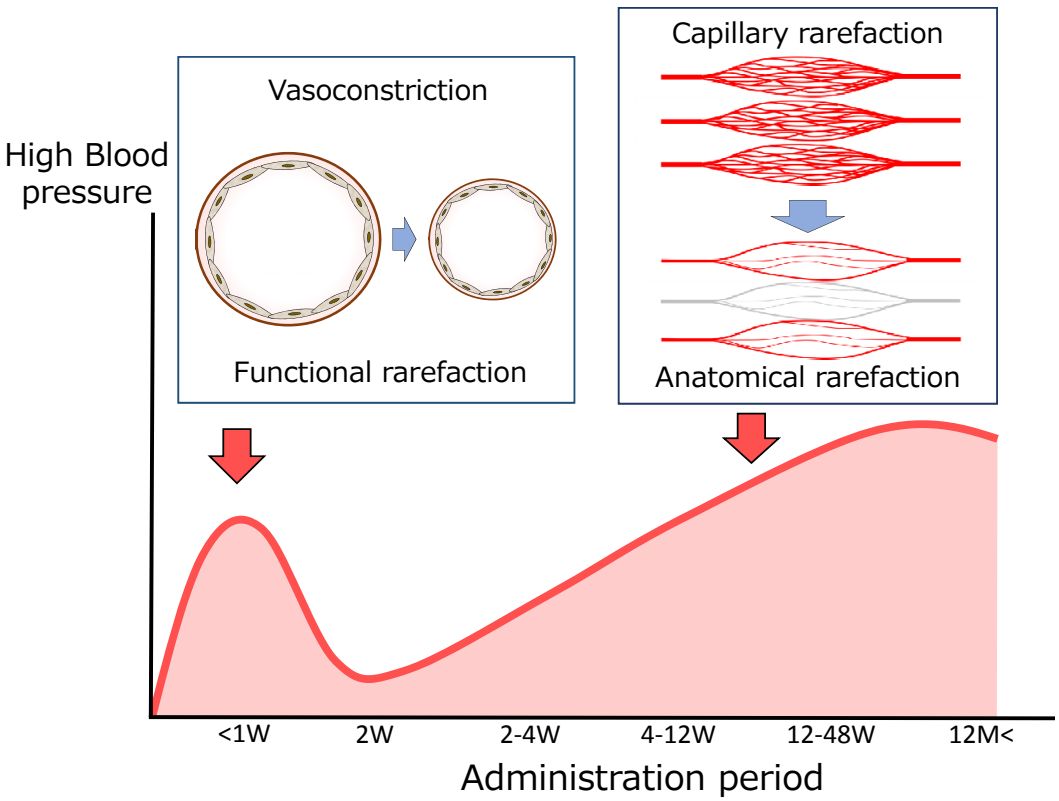

Fig. 2. Timing and mechanism of hypertension caused by anti-VEGF treatment

During the early phase of treatment with anti-VEGF drugs, blood pressure is increased by vasoconstriction caused by disturbance of NO and PGI_2 (functional rarefaction). This change occurs immediately after starting treatment in some patients and is irreversible. However, plaque is formed during long-term treatment, resulting in microangiopathy (capillary rarefaction). Peripheral vascular resistance increases, resulting in irreversible changes (anatomical rarefaction).
Quoted from the following articles:
(20) de Jesus-Gonzalez N et al. Hypertension. 2012; 60: 607-615.
(21) Mourad JJ et al. Annals of Oncology 2008; 19: 927-934.
(22) Takada M et al. International Heart Journal 2018 (in press).

fibroblast growth factor (FGF), and angiopoietin-1[23]. The receptors of these factors are important targets for molecular-targeted drugs. Multi-targeted tyrosine kinase inhibitors (TKIs) are anticancer drugs that were developed to target VEGF and other angiogenesis receptors. Chronic myeloid leukemia (CML) is a representative disease for which TKIs are used. Because more than 90% of CML cases are caused by a Philadelphia chromosome abnormality, the Bcr-Abl tyrosine kinase inhibitor imatinib was developed as first-line treatment and has markedly improved outcomes in patients with CML[24]. Second-generation TKIs such as dasatinib, nilotinib and bosutinib were developed to treat patients with imatinib-refractory disease. Ponatinib was developed to manage the most intractable Bcr-AblT315 mutations, enabling remission to be induced in most patients with CML[25].

On the other hand, the occurrence of arterial thromboembolism in patients with CML who receive TKIs has received considerable attention. In the PACE trial, assessing the clinical outcomes of treatment with ponatinib in patients with Bcr-Abl T315I mutations, the occurrence of arterial thromboembolism received considerable attention. The incidence of serious arterial occlusion was high (20%). More specifically, the incidence of cardiovascular thromboembolism was 16%, cerebrovascular occlusion 13%, peripheral vascular occlusion 14%, and venous thromboembolism 6%[26, 27].

Apart from ponatinib, dasatinib causes hypertension, pulmonary arterial hypertension (PAH), and platelet dysfunction. Nilotinib causes hypertension, peripheral arterial disease (PAD), ischemic heart disease (IHD), cerebrovascular accidents (CVA), hyperglycemia, and dyslipidemia. Bosutinib causes hypertension. These findings indicate that each drug has different cardiotoxicity profiles. Many aspects of mechanism of cardiotoxicity caused by TKIs several years after starting treatment remain unclear. However, cardiotoxicity caused by treatment for CML was characterized by a high

Table 2. The target sites of Bcr-Abl tyrosine kinase inhibitors and cardiotoxicity in patients with chronic myelogenous leukemia

Kinase/TKI	Imatinib	Nilotinib	Dasatinib	Bostinib	Ponatinb
Bcr-Abl	+	++	++	++	++
Bcr-Abl (T315I)					++
VEGFR				++	++
FGFR				++	++
PDGFR	+	+	++		++
SRC			++	++	+
DDR1	+	+	++		
Tie2					++
cKIT	+	+	++		++
Cardiotoxicity/TKI	**Imatinib**	**Nilotinib**	**Dasatinib**	**Bostinib**	**Ponatinb**
PAOD		++		+/−	++
IHD/CVA		+			+
VTE					+
Pulmonary hypertension			+		
Platelet dysfunction			+		+
Hypertension				+	++
Hyperglycemia	a	+			
Dyslipidemia	a	+			

Bcr-Abl tyrosine kinase inhibitors used to treat chronic myelogenous leukemia have multiple target sites, and each drug is associated with different cardiovascular adverse reactions.
a: Imatinib has been shown to have positive effects on glucose blood levels, as well as lipid profile.
Abbreviations: CVA: cerebrovascular accident, DDR1: discoidin domain receptor 1, HT: hypertension, IHD: ischemic heart disease, PAOD peripheral arterial occlusive disease, PDGFR: platelet-derived growth factor receptor, TKI: Tyrosine kinase inhibitors, EGFR: vascular endothelial growth factor receptor, VTE: venous thromboembolism.
Quoted from the following articles:
(28) Moslehi JJ, Deininger M. J Clin Oncol 2015; 33: 4210-4218.
(29) Pasvolsky O et al., Cardio-Oncology 2015; 1: 5-15.

remission rate as well as by long-term treatment with TKIs for several years or longer. This is also related to the fact that TKIs have multiple targets as shown in **Table 2**. Besides VEGFR, TKIs target PDGFR, discoidin domain receptor 1 (DDR1), SRC, and cKIT. Besides these targets, various factors, including FGF, HGF, and Tie-2 are known to be extensively disturbed as targets of angiogenesis[28, 29]. It is extremely interesting that imatinib is virtually free of cardiovascular adverse reactions, despite having nearly the same targets[30]. Ponatinib is a potent inhibitor of VEGFR1-3, but has a different cardiotoxicity profile from that of sunitinib and sorafenib, which can strongly inhibit VEGFR 1-3. Cardiotoxicity is thus considered to involve not only on-target factors, but also off-target factors. New findings obtained from the cardiotoxicity caused by cancer treatment are expected to suggest that cardiotoxicity involves not only on-target factors, but also off-target factors. Such new findings obtained from the cardiotoxicity of these anticancer treatments suggest that studying differences in and the target sites of these drugs might provide new important clues to the mechanism of atherosclerosis[31-33].

4. Immunotherapy and Cardiovascular Disorders

The development of immune checkpoint inhibitors has completely changed the conventional concept of anticancer therapy. Immune checkpoint inhibitors targeting CTLA4 or PD-1/PD-L1 have improved outcomes in many types of cancer. On the other hand, immune-related adverse events (irAE), associated with different characteristics and mechanisms from those of conventional anticancer treatment, have been reported[34-36]. Important cardiovascular irAE include myocarditis, pericarditis, vasculitis, and venous thrombosis[37-39].

In the cancer microenvironment, sites of cancer cell

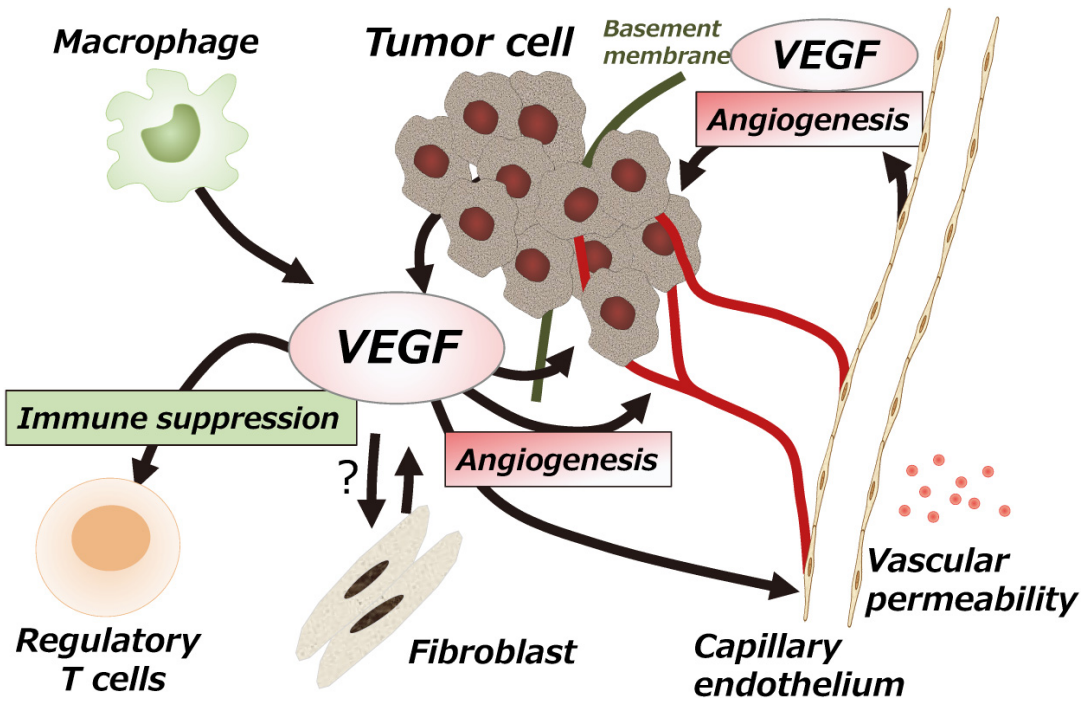

Fig. 3. Multiple mechanisms of VEGF in the tumor microenvironment

Vascular endothelial growth factors (VEGF) have multiple functions in the tumor microenvironment. VEGF secreted by vascular endothelial cells modulates factors such as endothelial cell proliferation during angiogenesis, reconstruction of the extracellular matrix, and vascular permeability, thereby maintaining the function of vascular endothelial cells. In contrast, in the tumor microenvironment, VEGF secreted by tumor cells acts to promote tumor cell infiltration and survival. VEGF also modulates tumor immune response by inhibiting dendritic cell function and regulating the function of suppressor T cells. The functions of VEGF are also related to tumor fibroblasts and macrophages.
Quoted from the following articles:
(40) Goal HL, Mercurio AM. Nat Rev Cancer 2013; 13: 871-882.
(41) Terme M et al. Caner Res 2013; 73: 539-549.

proliferation are associated with neovascularization, and VEGF is associated with anticancer immune response in contrast to conventional angiogenesis. As shown in Fig. 3, cancer cells create a microenvironment that allows them to avoid cancer immune surveillance along with tumor-reactive T cells, thereby allowing cancer-cell proliferation and metastasis. At that time, VEGF has accumulated in many cancers, and VEGF produced by these tumors can directly disturb the maturation of dendritic cells (DC) and activate antigen-specific regulatory T cells (T-reg)[40-44].

In combination immunotherapy using these characteristics, combining angiogenesis inhibitors with immune checkpoint inhibitors has been reported to have good outcomes[45, 46]. In the future, angiogenesis inhibitors might play a different role from the conventional role in immunotherapy-based anticancer treatment. On the other hand, measures are needed against irAE caused by immune checkpoint inhibitors and cardiotoxicity such as vascular disorders and thromboembolism caused by concurrent treatment with angiogenesis inhibitors.

5. Management of Drug-Induced Atherosclerosis

The diagnosis and treatment of drug-induced atherosclerosis in patients with cancer is challenging because the treatment of cancer has priority. Although ponatinib is associated with a high rate of serious cardiovascular complications exceeding 10%, patients who have CML associated with T315I mutations have refractory and fatal disease requiring treatment with ponatinib. Early treatment, including measures to prevent serious atherosclerosis, is therefore essential to appropriately treat cancer in patients with CML. Angiogenesis inhibitors are known to dose-dependently cause cardiotoxicity. Moreover, among patients who received ponatinib, the presence of 2 or more risk factors, such as advanced age, hypertension, diabetes mellitus, and dyslipidemia, was associated with high incidences of vascular disorders. The risk of cardiotoxicity should thus be evaluated by assessing cardiovascular risk factors and stratifying the cardiovascular risk[47].

Aspirin and statins are currently considered pro-

phylactic treatment for cardiotoxicity caused by cancer therapy-related atherosclerosis. Patients with many risk factors for atherosclerosis who are at a high risk for thrombosis should be considered candidates for treatment with aspirin and statins. Although treatment with antiplatelet drugs plus oral anticoagulants does not reduce the risk of cardiovascular events in patients with PAD[48], treatment with aspirin, which has antiplatelet activity, plus statins to prevent vascular endothelial dysfunction is considered relatively safe in patients with cancer. However, the management of cancer-associated thrombosis remains poorly understood. Long-term antithrombotic therapy including new anticoagulants to reduce the risks of thrombosis and bleeding should be considered[49]. In the near future, the advent of angiogenesis inhibitors and immune checkpoint inhibitors and the effectiveness of these treatments will increase the need for treating patients with chronic cancer and cancer survivors. The long-term outcomes of survivors of breast cancer after treatment are known to depend largely on atherosclerotic changes[50], and the surveillance and treatment of atherosclerotic lesions after the treatment of cancer have received considerable attention. Further studies including the close monitoring of further patients and intervention by cardiologists are needed[51, 52].

Conclusions

The development of new cancer treatments has caused a paradigm shift in the diagnosis and treatment of cancer, which may have an impact during the next 20 to 30 years. Conventional short-term anticancer and palliative therapy should be reconsidered. In patients with cancer therapy-induced atherosclerosis, continuous surveillance should be performed for longer periods than those initially planned in clinical trials currently in progress. It is expected that new knowledge not only about the effectiveness for cancer, but also about long-term adverse effects will be obtained. Long-term toxic effects should be minimized, thereby allowing cancer therapy to be appropriately maintained.

Conflict of Interest

The author (M.M.) has received lecture and manuscript fees from Daiichi Sankyo Company, Ltd, Bayer Yakuhin, Ltd, Bristol-Myers Squibb, Pfizer Japan Inc. and research funds from Bayer Yakuhin, Ltd, Bristol-Myers Squibb, Novartis pharma KK.

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