



Cardiovascular Side-Effects of Modern Cancer Therapy

Manabu Minami, MD, PhD; Shigemi Matsumoto, MD, PhD; Hisanori Horiuchi, MD, PhD

Recent advances in chemotherapy have substantially improved the prognosis of cancer patients. However, many anticancer drugs, especially newly developed 'molecular-target drugs', such as the anti-HER2 blocking antibody and the anti-vascular endothelial growth factor antibody, have serious cardiovascular side-effects such as heart failure, thromboembolism, severe hypertension and lethal arrhythmia, which interrupt cancer treatment and decrease the patient's quality of life. Despite the increasing clinical significance, cardiologists have not been focusing enough of their attention on this issue. The major cardiovascular complications associated with anticancer drugs, and current diagnosis, treatment and prevention strategies are reviewed. Close collaborations between oncologists and cardiologists is necessary to tackle cardiovascular complications and advance cancer treatment. (*Circ J* 2010; **74**: 1779–1786)

Key Words: Cancer; Cardioncology; Cardiotoxicity; Chemotherapy

Over the past few decades, cancer treatment has dramatically evolved. The development and implementation of intensive anticancer treatments have substantially improved the prognosis of cancer patients. Among the recently advanced cancer therapeutic modalities, the progress of chemotherapy is striking.

Significant efforts to explore the molecular mechanism of cancer development and progression have recently born fruit, in the so-called 'molecular-target drugs'. Most are either antibodies against cell surface proteins or small molecule protein kinase inhibitors. These drugs bring great promise, especially for advanced or recurrent cancers. Today their application is widening and producing excellent clinical outcomes. Furthermore, many new agents are currently under development for clinical use.

On the other hand, adverse side-effects of these cytotoxic drugs are inevitable, and some exhibit specific and potentially lethal side-effects on the cardiovascular system. Until recently, we have only needed to consider a few well-described examples of cardiotoxicity of anticancer drugs, such as those accompanying the anthracycline antibiotics. However, now we must also be mindful of the cardiovascular side-effects of these novel molecular-target drugs (Tables 1, 2). Both the prevalence and impact of cardiovascular toxicity, including unexpected adverse effects, are expanding. The assessment of a patient's cardiovascular condition and risks throughout chemotherapy, even years after completion of treatment, has become quite important.

With only a few exceptions, most of the molecular mechanisms that lead to cardiovascular toxicity during cancer treatment remain unclear. Anticancer drugs influence or disrupt

pathways that are centrally involved in cell survival, cell growth, inflammatory activation, and angiogenesis (Figure 1), which can spontaneously result in cardiovascular side-effects. Therefore, research on cancer treatment-associated cardiovascular side-effects may unveil novel molecular mechanisms that lead to heart failure, atherosclerosis, thrombogenesis, cardiomyocyte regeneration, and arrhythmia.

We review the major cardiovascular complications associated with cancer chemotherapeutic agents that current cardiologists should know about. Oncologists and cardiologists must collaborate closely to further improve the prognosis and quality of life of cancer patients. As was recently proposed, it is time that we explored the interdisciplinary field termed 'cardioncology'.¹

Cytotoxic Agents

Anthracycline Antibiotics

The most notorious, but best studied, cardiovascular side-effects associated with cancer chemotherapies are those induced by the anthracyclines, including doxorubicin, daunorubicin, epirubicin, and idarubicin, which are approved and widely used to treat leukemia and many soft tissue tumors. Anthracyclines accomplish their antitumor activity by intercalating into nuclear DNA, impairing transcription and cell division, inhibiting topoisomerase II activity, producing reactive oxygen species (ROS), and further injuring DNA as well as cell membranes and mitochondria.²

Anthracycline-mediated cardiomyocyte damage is cumulative, dose-dependent, and thought to occur through several mechanisms,^{3–5} but mainly through oxidative stress or free

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Department of Clinical Innovative Medicine, Translational Research Center (M.M.), Outpatient Oncology Unit (S.M.), Kyoto University Hospital, Kyoto; and Department of Molecular and Cellular Biology, Institute of Development, Aging and Cancer, Tohoku University, Sendai (H.H.), Japan

Mailing address: Manabu Minami, MD, PhD, Department of Clinical Innovative Medicine, Translational Research Center, Kyoto University Hospital, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: mminami@kuhp.kyoto-u.ac.jp

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ventricular or ventricular premature contractions, although they rarely become a serious clinical problem.⁶

The incidence of congestive heart failure (CHF) because of repeated anthracycline administration typically occurs within 1 year after completing the treatment, and depends on the cumulative dose. A report in 1981⁹ showed that the incidence of doxorubicin-induced CHF was 0.14% with total doses less than 400 mg/m² body surface-area, whereas the incidence increased to 7% at a dose of 550 mg/m² and to 18% at a dose of 700 mg/m². In that early study, there was a clear dose-dependent response, with a rapid increase in cardiac toxicity at doses greater than 550 mg/m². Thus, cumulative doxorubicin doses of 550 mg/m² are empirically considered a limiting dose to avoid doxorubicin-induced cardiotoxicity. However, in some races, especially the Japanese, there are no data regarding the association of cumulative doses of anthracyclines and the incidence of CHF.

It is noteworthy that diastolic dysfunction, although generally asymptomatic and subclinical, is considered to start even at cumulative doxorubicin doses of 200 mg/m².¹⁰ Several risk factors that potentially increase cardiac toxicity have been identified, including age, prior chest irradiation, the concurrent use of other anticancer drugs such as cyclophosphamide, trastuzumab, and taxanes, female sex, preexisting heart disease and hypertension.⁶ Careful consideration must be given when treating patients with these risk factors, even when the patients have received low cumulative doses of anthracycline. Furthermore, anthracycline-mediated cardiotoxicity is not only a risk for elderly patients but also children.

Late-onset cardiac dysfunction, which manifests several years to decades after anthracycline treatment, has been increasingly recognized, often in patients who were treated for cancer during childhood or adolescence. Notably, it was reported that late-onset cardiotoxicity impaired the prognosis of 5–10% of cancer patients who received anthracycline-containing chemotherapy and would have otherwise been in remission.¹¹ In other reports, late-onset anthracycline-induced left ventricular (LV) dysfunction occurred in 18–65% of patients;^{12,13} however, the incidence of severely reduced LV function increased with the duration of the follow-up period, suggesting that late-onset cardiac dysfunction is progressive. Aside from heart failure, it is noteworthy that life-threatening arrhythmias and sudden death have been reported in patients more than 15 years after they were treated with anthracycline.¹⁴

Although the mechanisms of late-onset cardiotoxicity remain unknown, progressive cardiomyocyte injuries that were initially caused by anthracycline must be involved in the delayed decompensation. Cumulative dose, higher rates of anthracycline administration, mediastinal irradiation, and female sex have been identified as risk factors for late-onset cardiac dysfunction. A recent study proposed that impairment of cardiac progenitor cells was involved in the pathogenesis of late-onset cardiotoxicity.¹⁵

Currently, early diagnosis and intensive treatment have greatly improved the prognosis of anthracycline-related cardiac failure. Nonetheless, certain patients with late-onset cardiomyopathy require cardiac transplantation.¹³

Taxanes

The taxanes, paclitaxel and docetaxel, are an important new class of anticancer agents that are widely used to treat breast and ovarian cancers. Interestingly, paclitaxel, which is introduced via a drug-eluting stent, has shown excellent clinical outcomes regarding in-stent restenosis. Taxanes exhibit their

anticancer effects by promoting polymerization of tubulin, leading to the development of dysfunctional microtubules and disturbing cell division.

Although most cases of paclitaxel-induced cardiac side-effects are subclinical sinus bradycardia (approximately 30%), paclitaxel may induce heart block with syncope, supraventricular or ventricular arrhythmias, and myocardial ischemia through unknown mechanisms.¹⁶ Importantly, taxanes potentiate anthracycline-induced cardiotoxicity by increasing the plasma levels of doxorubicin, and by promoting the formation of the toxic alcoholic metabolite, doxorubicinol, in cardiomyocytes.¹⁷ Docetaxel shows less cardiac toxicity than paclitaxel.

Fluoropyrimidine

5-fluorouracil (5-FU) is widely used to treat many solid cancers, including gastrointestinal, gynecological, head and neck cancers. Although acute heart failure, arrhythmia, and ECG changes have been associated with 5-FU treatment, the most commonly described and severe cardiac side-effect is myocardial ischemia, which varies clinically from angina to acute myocardial infarction.¹⁸ A previous report demonstrated that the frequency of cardiac events, including acute coronary syndromes, was 7.6% and the mortality rate was 2.2% after continuous intravenous infusion of a high dose of 5-FU.¹⁸ Patients with a history of coronary artery disease had a higher incidence of ischemic adverse events.^{19,20} Although the etiology is still unknown, it is thought that the cardiovascular toxicity is related to endothelial dysfunction and vasospasm of coronary arteries.¹⁹

Capecitabine, an oral prodrug of 5-FU, may also elicit myocardial ischemia and ventricular arrhythmias, although it appears to have less toxicity than 5-FU.²⁰

Cyclophosphamide (CPA)

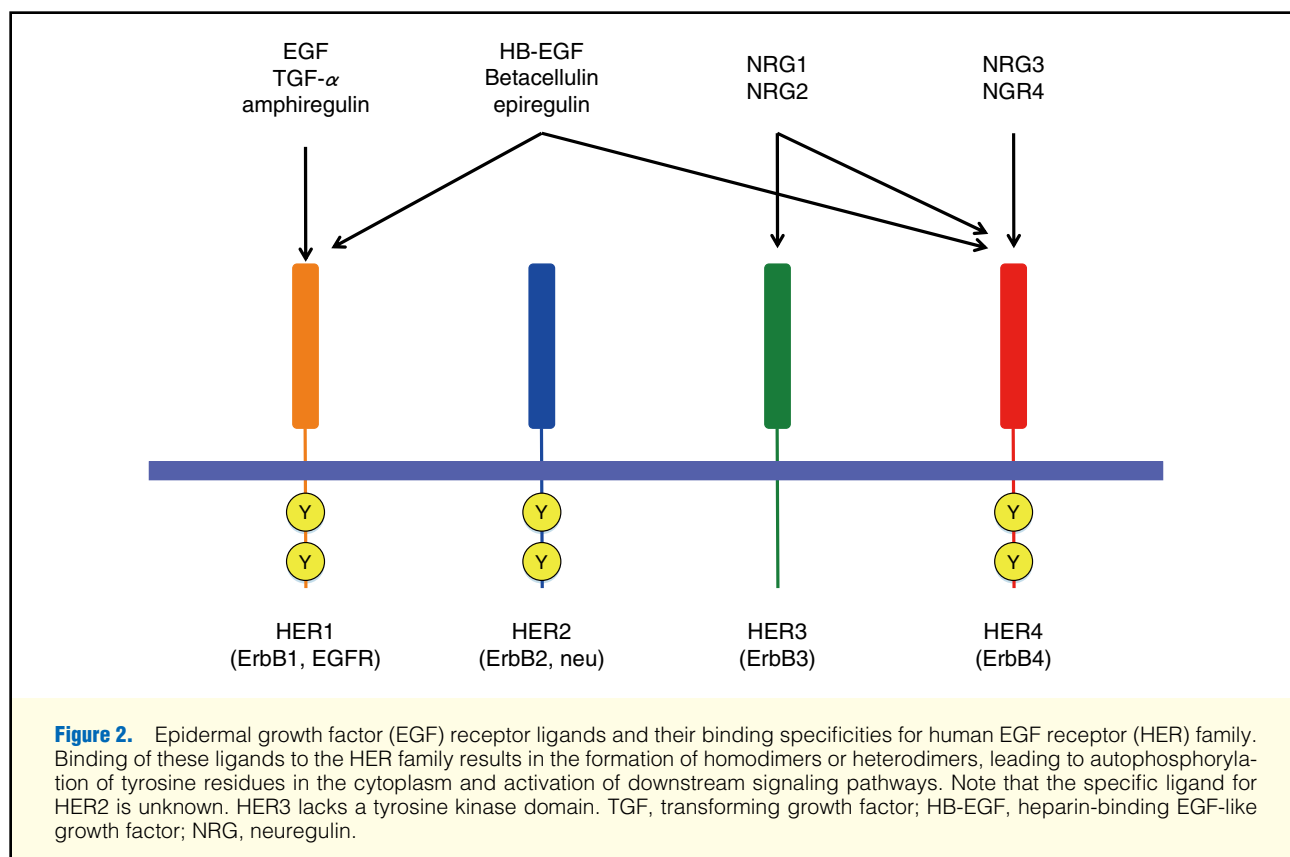
CPA is a common and classical alkylating agent that is widely used in the treatment of leukemia and many solid tumors, including lung, gastrointestinal, gynecological, skin and pharyngeal cancers. In addition, CPA is often used for the treatment of autoimmune diseases refractory to steroid treatments. Hemorrhagic cystitis is a well-known side-effect of cyclophosphamide administration.

CPA is generally well tolerated in terms of cardiovascular toxicity. However, high-dose rapid administration (eg, initial therapy for bone marrow transplantation) may induce lethal acute pericarditis and hemorrhagic myocarditis.²¹ Although the etiology of this complication is not fully understood, direct oxidative cardiac injury has been implicated. Unlike the anthracyclines, the toxicity associated with CPA appears to be related to a single dose and not cumulative doses. In addition, patients who previously received anthracyclines or underwent chest irradiation are more likely to suffer from CPA-induced cardiotoxicity.²²

Cisplatin

Cisplatin (CDDP) is a chemotherapeutic agent also used widely in the treatment of solid tumors, including lung, gastrointestinal, urinary, gynecological, head and neck cancers. The mechanism of the anticancer action of CDDP is not fully understood, although binding to DNA leads to the formation of inter- and intrastrand cross-links, resulting in impaired DNA synthesis and replication, further inducing cell death.

Dose-limiting side-effects of CDDP include ototoxicity, neurotoxicity, and nephrotoxicity because of renal tubular cell injury. With regard to cardiovascular complications, the



pre- and post-therapy hydration that are necessary with CDDP administration to avoid the irreversible nephrotoxicity potentially induce hypertension, resulting in exacerbated heart failure. Major cardiac events, including myocardial ischemia, have been reported to occur more than 10 years after CDDP-containing chemotherapy.²³ In addition, CDDP-associated nephrotoxicity can lead to a serum electrolyte imbalance, such as hypokalemia or hypomagnesemia, and possibly induce cardiac arrhythmia.

Molecular-Target Agents

HER2 and HER1/EGFR: Antibodies

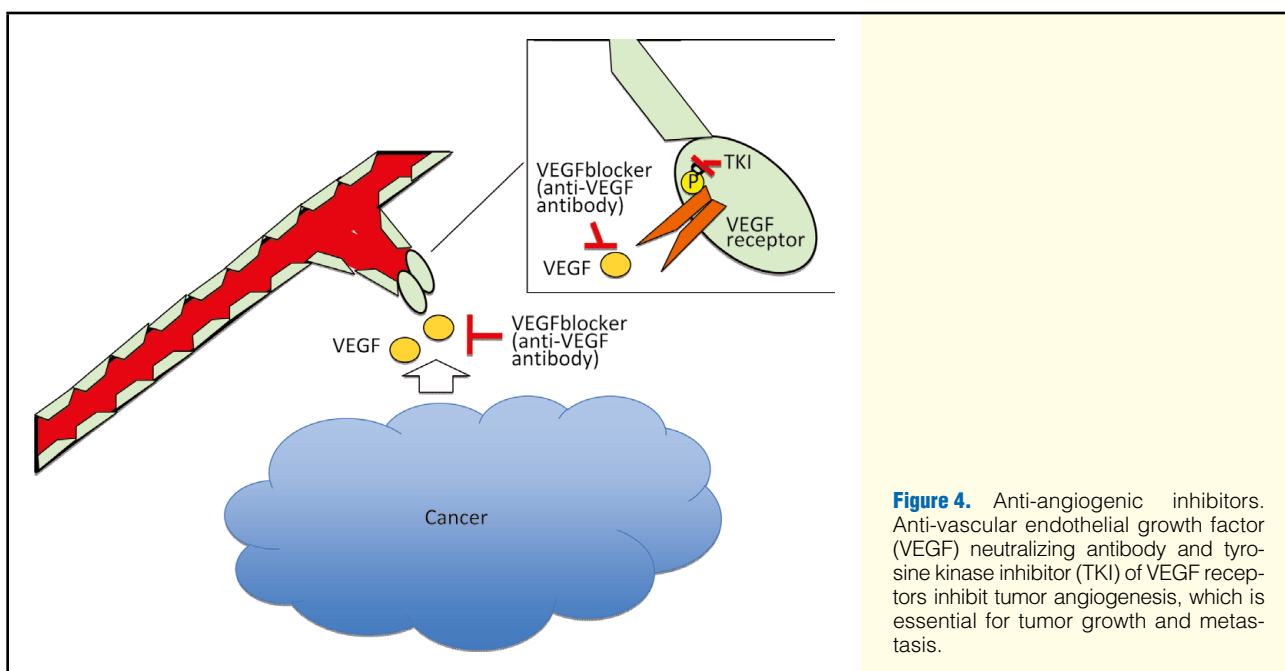
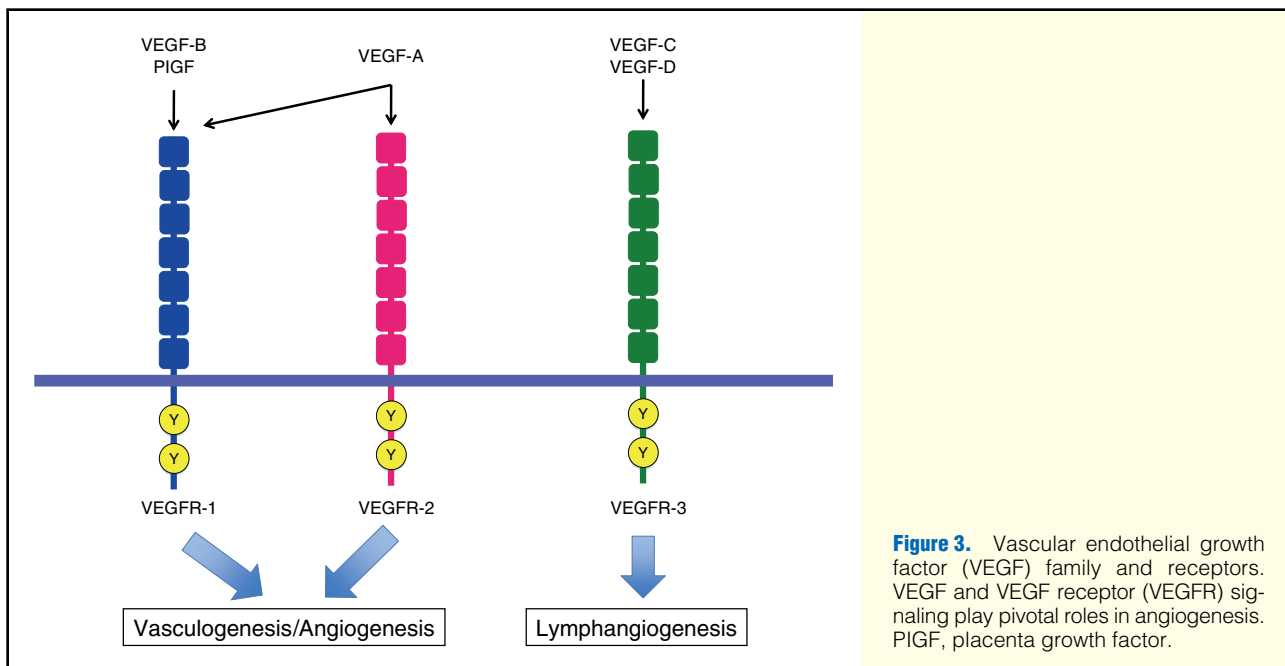
Trastuzumab Human epidermal growth factor receptor-2 (HER2) is a transmembrane receptor tyrosine kinase also known as ErbB2 or neu. Approximately 20–30% of breast cancers have augmented HER2 expression, which is associated with a poor prognosis.²⁴ Trastuzumab is an effective humanized IgG1 monoclonal antibody directed against the HER2 protein and is currently used as a central treatment for HER2-positive breast cancers.²⁵

It is well documented that trastuzumab induces LV dysfunction and heart failure, especially when it is administered in combination with anthracyclines.²⁶ In the initial phase I–II studies, a single-use of trastuzumab resulted in a low incidence of heart failure or LV dysfunction (4–7% of patients).^{25,27} However, a subsequent phase III study reported that administering trastuzumab in combination with anthracyclines and CDDP increased the overall incidence of cardiac dysfunction to 27%, with severe heart failure in 16% of patients²⁸ (8% and 3% of patients not treated with trastuzumab experienced cardiac dysfunction and heart failure, respectively).

Likewise, paclitaxel and trastuzumab combination therapy resulted in symptomatic or asymptomatic cardiac dysfunction in 13% of patients, whereas paclitaxel alone resulted in overall cardiac dysfunction in 1% of patients.²⁸

The mechanisms that lead to these complications are not fully understood, but HER2 signaling is thought to be pivotally involved in development of the embryonic heart and in maintaining postnatal cardiac function.²⁹ Although no specific ligand for HER2 has been identified, HER2 can heterodimerize with the HER4/ErbB4 receptors in the adult myocardium. Cardiac endothelial cells produce neuregulin-1 (NRG1), which binds to HER4 and promotes its heterodimerization with HER2 (Figure 2). The HER2/HER4 heterodimer subsequently activates various intracellular signaling pathways, including the PI3-kinase/Akt, MAP kinase, Ras, Raf and Grb2, which are essential for cell growth, glucose uptake, and the turnover of sarcomeric proteins.³⁰ Mice with targeted disruption of the *HER2*, *HER4* or *NRG1* genes are embryonically lethal because of aberrant cardiac development.^{31–33} Additionally, ventricular-restricted HER2-deficient conditional mutant mice developed dilated cardiomyopathy, and cardiomyocytes isolated from these mice were susceptible to anthracycline-induced toxicity.³⁴ In addition, immune reaction contributes to trastuzumab-mediated cardiac dysfunction because trastuzumab facilitates antibody-dependent cell cytotoxicity.³⁵

Aside from prior or concurrent exposure to anthracyclines, other potential risk factors are associated with trastuzumab-related cardiac side effects, including baseline LV ejection fraction (LVEF), prior cardiac diseases, elderly age and previous chest irradiation.^{36,37} Patients predisposed to cardiovascular risk factors (eg, smoking, hypertension, dyslipidemia, diabetes, and obesity) are more likely to experience cardiac



damage after trastuzumab treatment.³⁶

Trastuzumab-induced cardiac dysfunction is often reversible. In the Herceptin Adjuvant Trial (HERA), withdrawing trastuzumab resulted in recovery of LVEF declines in 69% of patients with significant and confirmed cardiac dysfunction.³⁶ Myocardial biopsy specimens revealed that, unlike anthracycline, there were no ultrastructural changes after trastuzumab administration.³⁸ In addition, the recurrence of trastuzumab-mediated cardiotoxicity is inconsistent: among 25 patients with a history of LVEF reduction because of trastuzumab, after appropriate treatment and recovery of LVEF, only 3 patients had repeated cardiac dysfunction with trastuzumab rechallenge.³⁸

Cetuximab Cetuximab, a human–mouse chimeric IgG1 monoclonal antibody that binds to the human HER1/EGFR, has recently been approved as a treatment for metastatic colorectal carcinoma. Cetuximab has been associated with thromboembolic adverse events, including myocardial infarction, pulmonary artery embolism, deep vein thrombosis and heart failure, although the incidence of those events was relatively low (2.5–4.8%).^{39,40}

HER2 and HER1/EGFR: Tyrosine Kinase Inhibitors (TKI)

Lapatinib Lapatinib is an orally active, small molecule TKI that targets HER2 and HER1/EGFR. Lapatinib is a promising treatment for patients with trastuzumab-resistant,

progressive breast cancer because it is effective against HER2p95 (truncated form of HER2)-positive cancer. Phase I–III trials (3,689 patients enrolled) that examined the cardiovascular safety of lapatinib found that 1.6% of patients had reduced LVEF by at least 20%, and 0.2% experienced symptomatic heart failure. Furthermore, the incidence of cardiac complications increased in patients who had previously received anthracyclines or trastuzumab.⁴¹

Vascular Endothelial Growth Factor (VEGF): Antibody

Under pathological conditions, tumors promote angiogenesis, which is essential for supplying oxygen and nutrition for rapid growth and metastasis. The critical regulators of tumor angiogenesis are VEGF and its receptors (VEGFRs) (Figure 3). Anti-VEGF neutralizing antibody and the small molecules that block the TK activity of VEGFRs may be rational anticancer agents and have been proven effective in many human cancers (Figure 4).

Bevacizumab VEGF-A is highly expressed in most solid tumors, including colorectal, lung, breast and renal cancers. Bevacizumab, a humanized IgG1 monoclonal antibody that binds to human VEGF-A and inhibits downstream signaling, is used to treat colorectal and non-small-cell lung cancers.

Newly developed or exacerbated hypertension is a major side-effect of bevacizumab. In clinical trials, grade 3–4 severe hypertension occurred in 9.2% of patients,⁴² with rare cases of hypertensive crisis, including encephalopathy or intracranial hemorrhage.

Thromboembolic events, such as myocardial infarction, ischemic cerebrovascular diseases, and pulmonary arterial embolism, are infrequent but life-threatening side-effects of bevacizumab that have been reported to occur in 3.8% of patients,⁴² and elderly patients (≥65 years) or those with prior arterial thromboembolic events may have a higher risk. Gastrointestinal perforation is also a rare (1–2%) but fatal adverse effect with bevacizumab treatment. Although the mechanisms are unclear, bowel ischemia is thought to play a part.⁴³

Regarding LV dysfunction, increasing cardiac toxicity has been associated with bevacizumab-based therapies in patients with advanced or metastatic breast cancer, many of whom were previously treated with anthracyclines.⁴⁴ Although there is little evidence for toxicity in this patient population, cardiac safety should be carefully monitored because bevacizumab-containing regimens are currently used to treat HER2-negative breast cancer.

Multiple-Target TKI

Sunitinib Sunitinib, a multiple target TKI, has recently been approved to treat metastatic renal cell carcinoma and gastrointestinal stromal tumors (GIST). Sunitinib inhibits tumor growth, metastasis, and pathologic angiogenesis.

When the cardiovascular safety of sunitinib was examined in phase I–II trials,⁴⁵ 11% of patients who received repeated cycles of sunitinib experienced cardiovascular events, including acute myocardial infarction and heart failure; 28% of patients showed an asymptomatic but significant reduction in LVEF of at least 10%. In addition, approximately half of the patients (47%) developed hypertension during sunitinib treatment. Patients with a history of coronary artery disease, LV dysfunction, or prior exposure to anthracyclines have been shown to be at increased risk for sunitinib-related cardiotoxicity, indicating that the cardiac conditions of this high-risk patient population should be monitored carefully.⁴⁶

Because it is unknown if LV dysfunction is reversible

after sunitinib therapy ceases,^{45,46} patients who experience significantly reduced LVEF should be monitored after they complete this therapy.

Sorafenib Sorafenib is a Raf kinase inhibitor that is also a multi-target TKI. The incidence of sorafenib-associated cardiac dysfunction is reportedly lower than that of sunitinib and appears to be reversible and responsive to general treatment.⁴⁷ In clinical trials of patients with renal cell carcinoma or solid tumors, severe hypertension occurred in 5.7% of patients treated with sorafenib and there was a 6.11-fold increase in hypertension in sorafenib-treated patients compared with controls.⁴⁸

Other Biological Agents

Imatinib Imatinib binds to the TK domain of the BCR-ABL fusion protein that activates cell proliferation in chronic myeloid leukemia (CML). Despite the excellent clinical outcomes, especially in CML or GIST patients, recent reports show that imatinib may increase the risk of heart failure.⁴⁹ Although imatinib-induced LV dysfunction is largely reversible after discontinuing the treatment, persistent and irreversible heart failure has also been reported.⁵⁰ Other than LV dysfunction, imatinib typically induces periorbital or peripheral edema through a non-cardiogenic mechanism with an unknown etiology.

Rituximab Rituximab, a chimeric mouse–human monoclonal antibody against the CD20 antigen, is now widely used to treat NHL. Most of the side effects associated with rituximab are infusion-related hypotension, arrhythmia, angioedema, and bronchospasms, which occur within the first few hours of treatment. The addition of rituximab to doxorubicin-containing standard chemotherapy significantly improves the response to therapy and reduces the risk of death in NHL patients, although potentiation of anthracycline-induced cardiotoxicity by the addition of rituximab is not detected, at least within the first year following therapy.⁵¹

Clinical Follow-up and Monitoring of Patients

The clinical course of cardiovascular side-effects of chemotherapy may vary from a transient, asymptomatic reduction in LVEF to cardiac death. To date, the plasma concentrations of troponin I and N-terminal pro-B-type natriuretic peptide, both of which are released from the heart in response to myocardial overload, have been demonstrated to be specific and sensitive markers for chemotherapy-induced cardiotoxicity.^{52–54}

Echocardiography is the most common and powerful tool to assess LV function. LVEF or fractional shortening is widely used and can definitively indicate cardiotoxicity associated with cancer chemotherapy. However, both of these methods depend on the preload and afterload at the time of evaluation, which can potentially lead to inconsistent values and assessments. Additionally, neither procedure is sufficiently sensitive to diagnose preclinical myocardial damage. From this perspective, Doppler echocardiography may be more powerful for detecting early cardiac toxicity.¹⁰ Exercise or dobutamine stress echocardiography and strain echocardiography may also be useful for the early detection of subclinical, latent cardiomyopathy that is related to cancer treatment. LVEF can be measured non-invasively and more precisely by radionuclide ventriculography or cardiac magnetic resonance imaging.

Cancer patients must be routinely evaluated for ECG abnormalities, such as ST-segment and T-wave changes, decreased

QRS voltage, and a prolonged QT interval. Furthermore, arrhythmias and conduction disturbances must also be carefully monitored. In particular, “torsades de points” associated with a prolonged QT interval because of anticancer drugs could be life-threatening.

Currently, endomyocardial biopsy is not routinely performed because it is invasive and has a higher risk of complications and possible sampling error.

Treatment

Once cardiovascular side-effects occur, patients must be treated with the appropriate medication. It is important to consider ceasing the anticancer treatment in accordance with the severity of the complications.

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type I receptor blockers (ARB), β -blockers, aldosterone antagonists, or diuretics should be administered as baseline CHF treatment. Although anthracycline-induced LV dysfunction is frequently irreversible, a recent clinical study indicated that enalapril (ACE inhibitor) and carvedilol (β -blocker; when possible) treatment resulted in a complete (42%) or partial (13%) recovery of LVEF, predominantly in patients in whom treatment was initiated at an early stage.⁵⁵ Similarly, for trastuzumab-related cardiotoxicity, administering an ACE inhibitor is currently recommended when LVEF declines to less than 50%.⁵⁶

For other severe cardiovascular complications elicited by anticancer therapy, including hypertension, arrhythmias, and thromboembolism, it is important to consider intensive and appropriate treatments in addition to interrupting the cancer chemotherapy. The renin-angiotensin system (RAS) may play a key role in vasoconstriction and lead to hypertension.⁵⁷ Therefore, inhibiting the RAS with an ACE inhibitor or ARB may be an optimal approach to manage bevacizumab- and angiogenic inhibitor-induced hypertension.^{42,58}

Prevention

To reduce the risk of anthracycline-induced cardiotoxicity, the cumulative dose should be limited and prolonged intravenous infusions should be considered instead of bolus administration. In addition, liposome-encapsulated anthracyclines have been developed to target cancer more preferentially and reduce the toxic effects on the heart. Some clinical trials have shown that liposomal anthracycline has less cardiotoxicity but provides similar antitumor efficacy.⁵⁹

Many clinical trials have shown that dexrazoxane, an iron chelator, effectively prevents the LV dysfunction that is induced by anthracyclines.⁶⁰ The FDA has approved dexrazoxane for clinical use in metastatic breast cancer patients who have received a cumulative doxorubicin dose of 300 mg/m², although Japan has not yet approved this clinical therapy.

Conclusion

The impact of cardiovascular side-effects on modern cancer therapy is becoming greater in our aging society, together with the clinical use of novel anticancer drugs. In the current clinical setting, it is likely that every cardiologist will face cardiovascular complications in cancer patients. Cancer also occurs more frequently in elderly people, who are more likely to be predisposed to cardiovascular diseases and this means that additional cardiovascular risks will occur in patients with cancer, and an increasing number of patients will have both

cancer and cardiovascular diseases.

Another point of consideration is cancer survivors. A recent retrospective cohort indicated that long-term survivors of childhood cancer have a 15.1-fold increased rate of CHF, a 10.4-fold higher rate of coronary artery disease, and 9.3-fold higher rate of cerebrovascular events compared with their sibling controls.⁶¹ Notably, the susceptibility of these survivors to overall cardiovascular diseases is greater than their risk of a second malignant neoplasm (14.8-fold increased risk compared with controls). Certainly, cancer treatment increases the risk of cardiovascular diseases, which requires that the long-term cardiovascular condition of each patient be followed over an extended time period, even if the cancer has been cured. Cardiologists should be aware of the potent cardiovascular complications that are related to cancer chemotherapy, and closely collaborate with oncologists to further advance cancer treatment and overcome the associated cardiovascular diseases.

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