Advancing The Cardiovascular Care in Cancer Patients on Chemotherapy

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ABSTRACT

Cardiotoxicity associated with chemotherapy, also known as Cancer Therapy-Related Cardiac Dysfunction (CTRCD), affects 10% of patients undergoing chemotherapy and is the most undesirable side effect of chemotherapy. Over time, it is anticipated that there would be an increase in the number of cancer patients receiving treatments that could harm their cardiovascular systems. Physicians should choose whether to continue, halt, delay, or reduce the dose of chemotherapeutic drugs to reduce the impact of cardiotoxicity.

Cardiotoxicity screening and diagnosis need a variety of methods, primarily echocardiography to evaluate Left Ventricular Ejection Fraction (LVEF) and Global Longitudinal Strain (GLS). Depending on the clinical state, these procedures may be carried out prior to, during, or following chemotherapy. It's critical to reduce cardiovascular risk factors and offer advice on leading a healthy lifestyle before giving cancer patients medicines.

There are a lot of cancer treatment facilities all around the world that don't have evidence-based perspective cardiotoxicity scores to stratify the risk of cardiovascular problems caused by cancer therapy. Additionally, comorbid conditions like diabetes and hypertension are frequently present in cancer patients, which can have a significant impact on clinical outcomes and cancer treatment. Therefore, this article aims to discuss assessment methods, clinical practice guidance, and prevention of CTRCD.

Keywords: *cardiac disease, cardiotoxicity, CTRCD, chemotherapy, cancer.*

INTRODUCTION

Cardiotoxicity associated with chemotherapy is a critical issue in cancer treatment. Cardiovascular disease and cancer are the two leading causes of morbidity and mortality, approximately contributing to 70% of death cases worldwide.[1] According to the Global Cancer Observatory data in 2020, there were 19.2 million newly diagnosed cases and 9.9 million cancer deaths. There were 396 thousand newly diagnosed cases and 234 thousand cancer death in Indonesia.[2] This situation is also observed in developed countries. Cardiovascular and cancer are diseases are also associated with high morbidity and mortality rates in the United States and Canada.[3–5] The International Agency

for Research on Cancer (IARC) estimates that globally, one in every five persons will develop cancer throughout their lifetime. Categorized by gender, the mortality proportions are one in every eight men and 1 in 11 women.[5]

The number of patients receiving cancer treatment that may impair the cardiovascular system is projected to continue increasing over time. In previous years, a study reported that post-curative treatment of breast cancer in postmenopausal women had higher risk of cardiovascular mortality than the cancer recurrence itself. Cardiotoxicity is assumed to be the cause mortality.[6] Cardiotoxicity, often identified with Cancer Therapy-Related Cardiac Dysfunction (CTRCD), is the most undesirable side effect of chemotherapy, impacting 10% of all patients. Cardiotoxicity is a process that begins with myocardial cells injury and followed by a reduction in Left Ventricular Ejection Fraction (LVEF), which leads to chronic heart failure if not treated properly.[7]

Early diagnosis of cancer and advancement of the treatment increase the survival rate.[6] To minimize the effect of cardiotoxicity, physicians should decide whether to continue, stop, postpone, or reduce the dose of chemotherapeutic agents.[6]

CHEMOTHERAPY IMPACT ON CARDIOVASCULAR

The administration of chemotherapy drugs must take into consideration both the potential adverse cardiovascular effects and the expected advantages.[1,8] Cardiotoxicity-related cancer therapy can result in severe cardiac dysfunction as a serious adverse effect. Cardiotoxicity affects the effectiveness of treatment, the quality of life, and overall survival in cancer patients.[8]

Cardiotoxicity due to chemotherapeutic agents is categorized into type 1 and type 2. The categories are made based on the effect of chemotherapeutic agents on cardiomyocytes. Type 1 cardiotoxicity is caused by irreversible cardiomyocyte cell death, either by necrosis or apoptosis. However, there is no cell death in type 2 cardiotoxicity. Type 2 toxicity is characterized by dose-dependent reversible cardiomyocyte cell damage.[9]

A common example of chemotherapy-related cardiotoxicity is the usage of anthracycline. Anthracycline-induced long-term cardiotoxicity results in the necrosis of cardiomyocyte cells and is thus classified as type 1 toxicity.[10,11] Anthracycline is one of the well-known chemotherapy agents, an anticancer drug with high effectiveness for solid tumors and hematological malignancies. However, due to the adverse cardiovascular effects, its usage is restricted. The mechanism of Left Ventricle (LV) dysfunction associated with anthracyclines has been previously investigated. The mechanism of the cardiotoxicity effect of Anthracyclines is the oxidative stress hypothesis, indicating that the reactive oxygen species and lipid peroxidation from cell membranes injure cardiomyocytes. However, this cardiotoxicity can be minimized to some extent by administration of protective agents (i.e., dexrazoxane).[12]

Anthracycline is widely known as a risk factor for induced heart failure (HF) and asymptomatic LV dysfunction.[13] Anthracycline cardiotoxicity can be divided into 3 categories based on the time of cardiotoxicity development: acute, subacute, and chronic. Arrhythmias (supraventricular tachycardias, ventricular ectopic beats), heart failure, and myopericarditis are examples of acute injuries that occur during or soon after administration of chemotherapy. Subacute cardiotoxicity develops within a few weeks. Myocarditis with edema and thickening of the left ventricular wall is a subacute clinical occurrence that contributed to diastolic dysfunction and increased mortality.[13,14]

An example of type 2 cardiotoxicity is the effect of trastuzumab, which is a HER2 inhibitors.[10] Uncertainty surrounds the mechanism underlying cardiomyopathy brought on by trastuzumab. According to some authors, it might be related to the HER2 receptor being present on the surface of cardiomyocytes. Cardiotoxicity, which manifests as heart failure and is accompanied by a decline in LVEF or an asymptomatic decline in LVEF, is one of the most frequent side effects of trastuzumab therapy.[15]

Combination chemotherapy for the treatment of solid tumors, leukemias, and lymphomas

frequently includes alkylating agents. It operates by impairing DNA transcription, which in turn causes a downregulation of protein synthesis. Although the exact mechanism of cardiotoxicity is uncertain, the most widely accepted explanation postulates that myocyte destruction and capillary microthrombi that encourage ischemia are caused by endothelium layer damage that allows potentially harmful compounds to flow into the myocardium.[9]

Antimicrotubule agents (taxanes) are frequently used to treat solid tumors. The method of action involves attaching to microtubules and preventing microtubule disintegration to prevent cell division. In comparison to other drugs, taxanes have a relatively low prevalence of LV dysfunction (0.7%). Taxanes alter the metabolism and excretion of anthracyclines, increasing the risk of cardiotoxicity.[9]

The presence of LV systolic dysfunction and congestive heart failure indicate the cardiotoxic effects of the chronic phase. Chronic cardiotoxicity can be categorized into two types: early type (symptoms arise within one year after chemotherapy) and late type (symptoms appear after one year of treatment completion). The mechanism of cardiotoxicity in the acute phase is believed to be different from that in the chronic phase, whereas the inflammatory process has a more significant role. The time-related course of cardiotoxicity differs between the pediatric group and the adult group, with the pediatric group developing cardiotoxicity during the chronic phase as chemotherapy doses accumulated. While in adults, this process occurs earlier and is affected by several comorbid cardiovascular risk factors, such as hypertension.[14] Early adverse events occur within the first year of treatment, while the late adverse events manifest after lengthy period (±7 years following treatment).[5,6] Biomarkers such as troponin I (TnI) and N-Terminal-prohormone Brain Natriuretic Peptide (NT-proBNP) can be used to monitor or identify cardiotoxicity. Aside from the chemotherapy agents mentioned above, **Table 1** shows the most prevalent cardiotoxicity adverse effects of anticancer drugs.[13]

Table 1. Cardiotoxicity side effects related to chemotherapeutic drugs.[13]

Manifested Cardiovascular toxicity	Associated chemotherapeutic drugs
Heart failure	Doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone, cyclophosphamide, ifosfamide, docetaxel, trastuzumab, bevacizumab, sunitinib, pazopanib, sorafenib, imatinib, dasatinib, lapatinib, nilotinib, carfilzomib, bortezomib.
Myopericarditis	Cyclophosphamide, 5-fluorouracil, cytarabine, trastuzumab, rituximab, Interleukin-2, Immune-checkpoint inhibitors.
Ischemic cardiomyopathy	5-fluorouracil, capecitabine, cisplatin, paclitaxel, docetaxel, etoposide, bevacizumab, sorafenib, sunitinib, bleomycin.
Atrial fibrillation	Cisplatin, cyclophosphamide, ifosfamide, melphalan, doxorubicin, capecitabine, 5-FU, gemcitabine, etoposide, paclitaxel, rituximab, sorafenib, sunitinib, ibrutinib, bortezomib, Interleukin-2, interferon.
Bradyarrhythmias	Cisplatin, doxorubicin, mitoxantrone, capecitabine, 5-FU, gemcitabine, paclitaxel, thalidomide, ifosfamide, bortezomib, epirubicin, Rituximab, cyclophosphamide, arsenic trioxide, interleukin-2, imatinib,
Accelerated atherosclerosis	Bevacizumab, nilotinib, ponatinib, carfilzomib, bortezomib.
Pericardial effusion	Cyclophosphamide, Immune-checkpoint inhibitors.
Venous thromboembolic disease	5-fluorouracil, cisplatin, nilotinib, ponatinib, erlotinib, bevacizumab, vorinostat, L-Asparaginase, immune-checkpoint inhibitors.
Arterial thromboembolic disease	Bleomycin, nilotinib cisplatin, carboplatin, vincristine, gemcitabine, bevacizumab, ponatinib, interferon alfa-2, immune-checkpoint inhibitors.
Arterial hypertension	Bevacizumab, sorafenib, sunitinib, axitinib, vandetanib, regorafenib.
Pulmonary hypertension	Dasatinib, cyclophosphamide.
Prolonged QT interval	Sorafenib, vorinostat, doxorubicin, axitinib, cabozantinib, dasatinib, lapatinib, crizotinib, sunitinib, nilotinib, ribociclib, arsenic trioxide, depsipeptide, vemurafenib, vandetanib.

CARDIOTOXICITY ASSESSMENT METHODS

Cardiotoxicity screening and detection require various methods.[12] Reduced LVEF has been widely used as a marker of cardiotoxicity. Among the several proposed criteria, the American Society of Echocardiography's is the most widely accepted. Cardiotoxicity is defined as a reduction in LVEF of more than 10% from the baseline to a final LVEF <53% in some clinical studies. Patients with remarkable reduced LVEF typically have poor prognosis.[9,16,17]

Advances in imaging modalities and the availability of cardiac biomarkers can contribute to early diagnosis, leading to a better quality of life in patients with cancer. Even though LVEF is the most well-known parameter to assess systolic function, LVEF has lower sensitivity to detect subclinical myocardial injuries. When a reduction in LVEF is observed in cancer patients, the myocyte cells are irreversibly damaged. As a result, other markers should be considered in order to detect subclinical cardiac toxicity earlier.[17]

The diagnostic criteria of cardiotoxicity defined by the European Society of Cardiology (ESC) are based on echocardiography, nuclear cardiac imaging, Cardiovascular Magnetic Resonance (CMR), and the use of cardiac biomarkers such as troponin, high-sensitivity troponin, BNP, and NT-proBNP.[16] Echocardiography is the method of choice for detecting myocardial dysfunction before, during, and after chemotherapy. Echocardiography can be performed in three dimensions (3D) or in two dimensions (2D) using the Simpson biplane method. The most frequently used imaging method for monitoring LVEF during and after chemotherapy is two-dimensional echocardiography. However, the intra and inter-observer variability is a major limitation. Therefore, 3D echocardiography has been recommended to be the best method for LVEF monitoring in cancer patients.[9]

The best modality to assess cardiotoxicity during or following chemotherapy is Global Longitudinal Strain (GLS). Global Longitudinal Strain can detect myocardial damage. An absolute reduction in GLS values of more than >-19% after completion of anthracycline therapy is considered a predictor for future cardiotoxicity (positive predictive value is 53% and negative predictive value is 87%).[18] The advantages of this modality are its wide availability, most negligible radiation, non-invasive method, its ability to assess hemodynamics, and its availability to be used for serial examination. However, the limitations of this modality include the poor image quality, skill requirements, as well as inter-observer and inter-vendor variability.[12,14]

Other than echocardiography, additional methods that can be used to diagnose cardiotoxicity, including Multigated Acquisition (MUGA) scanning and cardiovascular magnetic resonance (CMR). For many years, MUGA, or nuclear cardiac imaging, has been used to diagnose chemotherapy-associated cardiotoxicity with high precision and reliability. However, the usage is usually hampered by radiation exposure and its limited ability to provide information about heart anatomy and hemodynamics. The diagnostic cutoff value for MUGA cardiotoxicity has been determined as a reduction in the ejection fraction value of more than 10% to 50%.[11]

Due to its excellent sensitivity and specificity, cardiovascular magnetic resonance (CMR) can be used to assess or retest echocardiographic test results that are unclear or inconsistent between one test and another. Another advantage of using CMR is the ability to evaluate more structures such as the pericardium or the presence of severe myocardial fibrosis. However, CMR is infrequently used because it is not available at every facility and requires high standardized resources.[11,13] Nuclear cardiology imaging can be used in addition to echocardiographic methods. The criterion of cardiotoxicity in this method is a reduction of more than 10% LVEF, with a LVEF value less than 50%. The advantage of this method is its reproducibility and its minimal inter-observer variability in evaluating LVEF. Meanwhile, the disadvantages of this modality include radiation exposure and limited information on the structure and function of the heart.[12,14,17] In addition to precisely estimate LV and systolic volumes with high reproductive function, CMR is also capable for detecting myocardial edema, perfusion abnormalities,

and fibrosis.[19] In addition, CMR requires patient adaptation (claustrophobia, continuous breathing, long acquisition time). It is used when other methods are on the verge of failing and require validation from this modality.[12,19]

The cardiac biomarker measurements consist of High Sensitivity Troponin I (HS-TnI), Troponin I, NT-ProBNP, and BNP. These serum markers are helpful in detecting acute cardiotoxicity. BNP, a unique cardiac neurohormone, is released as the ventricular response to increased wall tension.[11,12] The primary role of NT-ProBNP and BNP in monitoring patients with high risk needs more investigation. The positive aspects of the method of cardiac biomarker measurements are its reliability, efficiency, accuracy, wide availability, and high sensitivity. The shortcomings include a lack of data to confirm the significance of changes, variances in the tests, and the role of periodic surveillance.[12] In general, the NT-proBNP level helps to assess initial risk stratification and predict the prognosis of LV dysfunction. Gradual changes of NT-proBNP throughout three days of chemotherapy are associated with progressive reduction in LVEF.[2,12,18,19]

Canadian Cardiovascular Society (CCS) guidelines recommend the same imaging method and modality to determine LVEF before, during, and after chemotherapy for cancer. Myocardial strain imaging can be used to detect early subclinical LV failure in cancer patients receiving potentially cardiotoxic drugs. The physician can also perform serial measurements of cardiac biomarkers.[6] A comparison of various modalities for assessing cardiotoxicity is described in the **Table 2**.

A multimodality strategy that incorporates multiple biological and imaging parameters might be useful for detecting cardiotoxicity. According to a study conducted by Sawaya et.al, the combination of an increase in hs-cTnI and a reduction in GLS >-19% has an 87% sensitivity to diagnose cardiotoxicity. However, when each parameter is used separately, the sensitivity values are 74% and 48%, respectively.[18] When paired with biomarker analysis, GLS > -17.5% and troponin T > 0.034 ng/ml have a specificity of 94%, indicating that it is a promising strategy for cardiotoxicity prediction.[20]

CLINICAL PRACTICE GUIDANCE

Before administering cancer medications, it is crucial to optimize cardiovascular risk factors and provide healthy lifestyle recommendations such as nutrition, smoking cessation, and exercise. Risk stratification and management of undesirable cardiovascular side effects in cancer treatment are two elements that physicians should consider when determining management actions. Cardiovascular risk stratification with HeartScore has been approved by the European Association of Preventive Cardiology (EAPC) to assist in the adjustment of cardiovascular risk factors.[17]

Table 2. Comparison of Diagnostic Modalities to Evaluate Cardiotoxicity[2,6,9,12–14,16]

	Echocardio-graphy 2D	Echocardio-graphy 3D	Strain Longitudinal Global	MUGA	CMR	Troponin I
Availability	++++	+++	+++	+++	++	+++
Reproducibility	++	+++	+++	+++	++++	++++
Radiation	Zero	Zero	Zero	5-10 mSv	Zero	Zero
Detection of Subclinical Toxicity	Low	Low	High	Low	Moderate	High
Additional Diagnostic Utilities	Structural information, valvular heart disease, pericardial disease, diastolic function				Characterizing tissue, pericardial disease	Has a high negative predictive value when combined with global longitudinal strains

MUGA: Multigated Acquisition. CMR: Cardiac Magnetic Resonance. mSv: millisievert.

Numerous cancer treatment centers throughout the world lack evidence-based perspective cardiotoxicity scores to stratify the risk of cancer therapy-related cardiovascular issues. However, data from clinical trials and registries allow us to identify high-risk groups. Cardiotoxicity related to anticancer therapy must be identified in future cardio-oncology research. In this regard, coordination between the cardiology and oncology departments is required. The present issue is whether the cardiotoxicity caused by cancer treatment is specific to the drugs or class of drugs.[8] Furthermore, because of a lack of long-term data on survival of the risk of cardiac dysfunction, no recommendations about the categorization-specific risks in cancer patients treated with anticancer against cardiotoxicity can be provided.[11,17]

Cardiologists have new challenges and responsibilities as part of this developing multidisciplinary cooperation. This involves optimum treatment of underlying cardiovascular risk factors as well as monitoring cardiac safety against cardiotoxicity.[11] The following are some monitoring strategies that can be implemented: Take a thorough medical history and physical examination to identify risk factors for cardiovascular disease (smoking, diabetes, hypertension, dyslipidemia, and obesity),[8] preexisting heart disease (cardiomyopathy, myocardial infarction, clinically relevant cardiac arrhythmias, moderate or severe valvular heart disease), and previous cardiotoxic treatments.[14]

Blood pressure monitoring is recommended every week during the first cycle of therapy and then every 2-3 weeks during anticancer therapy.

Electrolyte monitoring throughout treatment must be considered at the start, 7-15 days after the dose is initiated or adjusted, every month for the first three months, and then on a monthly basis for the next three months, depending on the chemotherapy agent and the patients' condition.[12]

Frequent electrocardiogram (ECG) helps detect early cardiotoxicity at baseline, every 2-4 weeks for the first three months, every three months for the next three months, and then regularly during therapy depending on the chemotherapy regimen and the patient's condition.

Cardiac biomarkers (troponin, natriuretic peptide) can be measured at the beginning of chemotherapy, followed by every 2-3 months, to help monitor cardiac tissue injury.[11]

Echocardiographic evaluations every 2-3 months will be helpful in the detection of LV dysfunction.[11] To avoid radiation in individuals with poor imaging quality, cardiac magnetic resonance is an option. Methods for monitoring must be customized to the availability of local resources during therapy. Professional expertise is required to minimize unnecessary delays in cancer therapy.[17]

All associated decisions should consider potential threats to life expectancy, quality of life, and risk of complications. Individualized management will depend on the clinical condition, characteristics, and the causative drug.[6]

COMORBIDITIES IN CANCER PATIENTS

Some anticancer therapies are known to have deleterious effects on the cardiovascular system. Although many health care providers are aware of the potential short-term cardiotoxicity associated with anticancer therapy, there is often a lack of concern for the long-term consequences of this treatment for cardiovascular health. Cancer patients often have comorbid diseases such as diabetes and hypertension, which can greatly influence cancer treatment and clinical outcomes.[1]

Myocardial ischemia and arrhythmia infarction caused by ischemia are adverse effects of several therapeutic cancers. Fluoropyrimidines, including 5-fluorouracil and capecitabine, are the most well-established cause of coronary arterial spasm leading to acute myocardial ischemia during cancer therapy.[14] The mechanism of this anticancer drug can cause myocardial ischemia and the development of premature arteriosclerosis. Prior to cancer treatment, it is critical to recognize and identify patients who have had past coronary artery disease (CAD) or other cardiovascular diseases. According to the most recent guidelines, the minimum period of dual antiplatelet medication should be pursued to a reasonable extent in patients treated by percutaneous coronary intervention who are subsequently confirmed to have malignancies to

reduce the risk of bleeding. Thrombocytopenia following chemotherapy makes multimodal treatment challenging. Medical therapy and intervention options are limited; even the use of antiplatelet and anticoagulant medications is sometimes difficult to do.[12] The key to identifying people with latent coronary artery disease is the clinical examination for myocardial ischemia. Regular ECG can be used to monitor myocardial ischemia. If cardiac ischemia occurs, chemotherapy must be put on hold and adjustments are required.[18]

The most common comorbidity in patients with malignancy is hypertension (37%). Before chemotherapy, the percentage is similar to that of the general population (29%).[11] The severity depends on the patient's age, history of hypertension, type of cancer, type of drug and dosage, the timing of use, and cancer-related therapy.[12] Evaluation of treatment compliance is needed when severe hypertension is present. Follow-up is essential to ensure improvement and antihypertensive drug tolerance. Vascular endothelial growth factor (VEGF) inhibitors are known to have an increased risk (11-45%) to induce new hypertension. To avoid interaction with VEGF inhibitors, those suffering from resistant hypertension should be sent to a cardiologist or have their blood pressure monitored.[21]

The goal of hypertension management is to diagnose hypertension (BP > 140/90 mmHg) while maintaining blood pressure stable (BP 140/90 mmHg or lower in the event of proteinuria). Before starting VEGF inhibitors, a first assessment of cardiovascular disease risk factors (including a history of hypertension and current blood pressure level) and arterial hypertension treatment must be performed. As first-line treatment, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and non-dihydropyridine calcium channel blockers (amlodipine, felodipine) can be used.[14]

Severe atherosclerotic and non-atherosclerotic Peripheral Arteries Disease (PAD) in the lower extremities can occur in up to 30% of patients who are getting cancer therapy. PAD can occur early in the first months of therapy or as an effect that is delayed several years after treatment. One recommendation is an initial PAD risk evaluation (assessment of risk factors, physical and clinical examination, measurement of the ankle-brachial index (ABI)). The Fontaine stages 1-2 (asymptomatic or with intermittent claudication) require risk control and periodic clinical, metabolic, and hemodynamic follow-up. Antiplatelet drugs should be considered primarily for symptomatic PAD. Revascularization can be considered for severe PAD at the beginning or during cancer therapy.[12]

Intra Arterial thrombotic incidents are uncommon in cancer patients, occurring at a rate of 1%. Antithrombotic treatment, thrombolysis, and/or endovascular intervention should be managed in a multidisciplinary consultation that includes a cardio-oncology team, if available. However, venous thrombosis and venous thromboembolism (VTE) are common in cancer patients, may occur in up to 20% of hospitalized patients, and are frequently underreported. They may be associated with chemotherapy, including the route of delivery (usage of permanent venous catheters), as well as the prior patient's malignancy and venous risk from thrombosis. Treatment of episodes confirmed by acute VTE in patients with stable hemodynamics consists of 3-6 months of Low Molecular Weight Heparin (LMWH).[12]

CONCLUSION

With a growing prevalence as cancer patients continue to rise, CTRCD is a serious problem in cancer therapy. Cardiotoxicity has an impact on cancer patients' overall survival, quality of life, and response to therapy. Several techniques are needed for cardiotoxicity screening and detection, even a multimodality approach including imaging and biological markers. Comorbid conditions like diabetes and hypertension are frequently present in cancer patients, which can significantly impact the clinical outcomes.

The administration of chemotherapeutic medications must evaluate both the anticipated benefits and any potential cardiovascular side effects. Clinical practice recommendations for cancer patients must be developed. Therefore,

because of this expanding multidisciplinary collaboration, cardiologists now face new challenges and responsibilities. Individualized treatment plans will be based on the clinical condition, its traits, and the substance that caused it.

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