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Effects of cancer treatments for the cardiovascular system: Occurrence, etiology, diagnostics, and treatment

Kavina Ganapathy[1], Devanshu J. Patel[2], Sulabh Mahajan[3], Suhas R. Mule[4], Vikram Shete[5], Jagtej Singh[6]

[1] Department of Biotechnology, School of Sciences, Jain (Deemed to be University), Bangalore, India
[2] Department of Pharmacology, Parul University, Waghodia, Vadodara, Gujarat, India
[3] Centre of Research Impact and Outcome, Chitkara University, Rajpura, Punjab, India
[4] Department of Cardiology, Krishna Institute of Medical Sciences, Karad, Maharashtra, India
[5] Department of UGDX, ATLAS SkillTech University, Mumbai, Maharashtra, India
[6] Chitkara Centre for Research and Development, Chitkara University, Himachal Pradesh, India

ABSTRACT

Chemotherapy, radiation, and surgery are all used in combination in modern cancer treatment to both extend the life and cure the disease. But a lot of these medications can lead to heart problems, myocardial infarctions, hypertension, thromboembolism, and arrhythmias, among other cardiovascular issues. This article analyzes the prevalence of cardiotoxicity caused by commonly used chemotherapy medications and discusses the etiology, diagnosis, treatment, and prevention of these cardiovascular adverse effects. Given that it might have a major impact on cancer patients' overall prognosis and survival, cardiotoxicity linked with anticancer therapy must be recognized. The aging cancer patient population and the advent of various novel cancer medicines will certainly make cardiotoxicity a substantial concern for future use by cardiologists and oncologists.

Keywords: cardiovascular system, cancer treatments, occurrence, etiology, diagnostics, and treatment

Address for correspondence:

Kavina Ganapathy

Department of Biotechnology, School of Sciences, Jain (Deemed to be University), Bangalore, India

E-mail: g.kavina@jainuniversity.ac.in

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INTRODUCTION

The treatment of cancer has advanced significantly in recent years, and there has been a great success in lowering the morbidity and mortality from a variety of cancer. The latest theory is that cancer is a treatable condition that can be controlled via early identification, routine monitoring, and coordinated treatment decision-making, much like high blood pressure or diabetes. Therefore, cancer survivors must keep their concomitant conditions to a minimum [1]. Heart illness will pose a greater danger to many cancer survivors than a recurrence of the disease. Radiation treatment, surgery, and ever-more-complex drug combinations are now available as therapeutic alternatives for cancer patients. The results for patients are likely to be significantly impacted by several of these therapies, many of which have major potential adverse cardiac consequences. Therefore, for these consequences to be effectively managed, recognizing them is essential. Over the past 20 years to 30 years, there is a significant decline in the death rate among cancer patients [2]. Although it has not previously been recognized, the toxicity of traditional cancer treatment, including radiation and chemotherapy, is a major contributor to morbidity and death in survivors. Rapid advancements in "targeted therapies" are being made, many of which have known or unknown cardiovascular side effects. Cancer therapy can cause cardiac toxicities (Figure 1).

Technological advances in cancer treatment, including radiation and systemic therapies, have improved the prognosis for people with malignancies [3]. They may, however, also have long-term effects, such as increasing the risk of Cardiovascular Disease (CVD) in long-term survivors. Cardiovascular Diseases (CVDs) are major causes of sickness and mortality in the general population, accounting for 30%–50% of all fatalities in the majority of developed nations. Given the high baseline frequency of CVD, even a little increase in risk will have a substantial impact on morbidity and death [4]. Heart disease that develops after cancer therapy may be brought on by the cancer treatment's direct effects on the circulatory system or by cardiovascular risk factors that hasten atherosclerosis. The unfavorable cardiac consequences of cancer therapy continue to be a major source of worry. At the height of the period of targeted cancer therapy, vascular toxicities were on par with cardiac toxicity in terms of scientific publications, but they have subsequently appeared as the second-most often documented cardiovascular hazard linked with cancer therapy (Figure 2). Importantly, among cancer patients receiving

outpatient therapy, vascular toxicities rank as the second most prevalent cause of mortality [5].

To attempt a synthesis of the corpus of information about the harmful effects of routinely used anticancer medications on the cardiovascular system. It looked up information on the potential cardiovascular side effects of each of the aforementioned chemotherapeutic medications on MEDLINE. The most current reviews and important studies describing the occurrence, etiology, and treatment of cardiovascular problems associated with chemotherapy were included. These anticancer treatments were left out of the evaluation if there were just case reports available or if the occurrence of a specific cardiotoxicity was thought to be unusual.

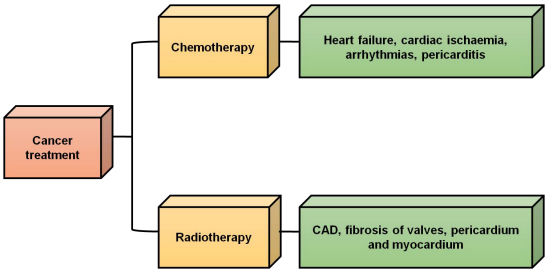

Fig. 1. Cancer treatment

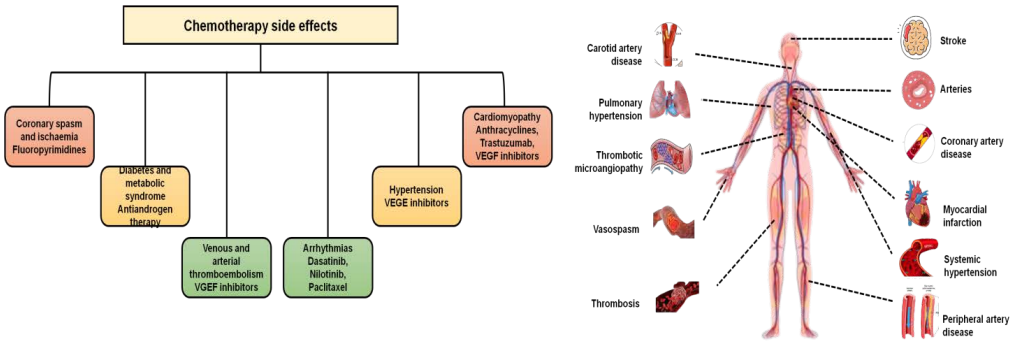

Fig. 2. Spectrum of vascular toxic effects of cancer therapies *vs.* Chemotherapy side effects

CASE 1

Thromboembolism

It is referred to that prothrombotic conditions are a side consequence of cancer. The patients most likely to develop thrombosis seem to be those with documented risk factors and advanced illness. Immobility, heart failure, atrial fibrillation, dehydration, and the use of chemotherapeutics at the same time as a central venous catheter are all associated with risk [6]. Table 1 summarizes the incidences of clinically significant Venous Thromboembolism (VTE) associated with certain chemotherapeutic agents.

Tab. 1. Chemotherapy and venous thromboembolism associated

Chemotherapy Agents	Occurrence	Frequency of Use
Alkylating Agents		
Cisplatin	8.4	+++
Angiogenesis Inhibitors		
Thalidomide	1-55	+
Lenalidomide	3-77	+
Small Molecule Tyrosine Kinase Inhibitors		
Erlotinib	3.10-12	+++
Histone Deacetylase Inhibitor		
Vorinostat	4.8-9	+

Occurrence

Cisplatin:

Patients with cancer have been demonstrated to have a higher risk of thrombotic events after receiving platinum-based treatment. 35 patients (11.9%) receiving cisplatin treatment for urothelial transitional cell carcinoma had vascular incidents. 23 individuals (8.5%) out of the 35 patients who had thromboembolic events had either a Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE).

Vorinostat:

4.7% of patients taking vorinostat develop thrombosis. However, 2 trials detailing the prevalence of thromboembolism related to vorinostat have been reported. The frequency of thromboembolic events was 5.4%, according to a phase IIb study including 74 individuals with CTCL.

Thalidomide:

Thalidomide is the chemotherapy drug that is most often linked to the onset of thromboembolic problems. Low occurrence of

thrombosis (5%), which is related to thalidomide monotherapy. But when thalidomide is administered to patients who have just been given a diagnosis, along with when it is combined with dexamethasone or chemotherapy, especially doxorubicin, without thromboprophylaxis, this risk rises sharply (3% to 58%). A thrombotic event linked to thalidomide often took three months or less to manifest [7].

Lenalidomide:

Lenalidomide is a thalidomide derivative that varies from the original molecule in that it has a more favorable toxicity profile. Lenalidomide seems to still have a significant risk of thrombosis, nevertheless. The occurrence of thromboembolism has been reported in clinical investigations to range from 3% to 75%. Lenalidomide does not substantially raise the risk of VTE when used alone. High dosages of dexamethasone and the use of erythropoietin are risk factors linked to higher rates of VTE. In one research, the occurrence was greatest (75%) in patients who had just been diagnosed.

Etiology:

The baseline hypercoagulable condition associated with malignancy is affected by several variables, such as the expulsion of a substantial quantity of inflammatory substances inflammatory compounds, restriction of natural anticoagulant treatment processes. The processes by which anticancer therapies cause thrombosis have not been fully elucidated due to the complexity of this condition, where many hemostatic disorders occur.

Cisplatin:

Therapies based on cisplatin may potentially change the integrity of endothelial cells. Finally, cisplatin may increase levels of von Willebrand factor, promote vasospasm brought on by hypomagnesemia, and have antiangiogenic effects.

Thalidomide and lenalidomide:

The direct impact of thalidomide on endothelial cells that have already been harmed by doxorubicin has been hypothesized to contribute to thalidomide-induced thromboembolism. Platelets and endothelium may potentially engage in this process. Patients who took thalidomide showed signs of increased von Willebrand factor and platelet aggregation. These identical processes could be in charge of lenalidomide's thrombosis since it is an analog of thalidomide.

Diagnosis:

Compression ultrasonography is the preferred diagnostic method for DVT because of its excellent sensitivity and specificity. Spiral computed tomography angiography is the preferred diagnostic procedure when PE is suspected. Less often used are nuclear medicine procedures like the ventilation/perfusion scan [8].

Prevention of thromboembolism

Thalidomide and lenalidomide:

Numerous prophylactic measures have been researched due to the possibility of thrombotic events. Since there haven't been any randomized, prospective studies directly comparing various anticoagulants, there aren't any established recommendations on how to treat these people. However, the International Myeloma Working Group only recently released advice on how to prevent myeloma patients from developing thrombosis linked to thalidomide and lenalidomide. An ideal prophylactic approach will be determined by ongoing randomized studies contrasting aspirin, warfarin, and LMWH.

Treatment of thromboembolism:

Once a VTE has been identified, therapy focuses on symptom relief, embolization avoidance, and recurrence avoidance.

Thalidomide and lenalidomide:

Although there is an ongoing debate about the ideal length of treatment, prolonged care is advised given the significant risk of recurrence (>10%) in cancer patients who have had VTEs one year after stopping the anticoagulant medication. Additionally, it is advised that after complete anticoagulation has been established, it is permissible to momentarily stop taking thalidomide or lenalidomide and then restart medication [9].

CASE 2

Hypertension

In the same patient, HTN and cancer often coexist. Furthermore, epidemiological research raises the notion that there is a connection between the two and that HTN influences cancer patients' overall prognoses. Modern cancer treatments block angiogenesis; therefore, people who receive them often get HTN. Table 2 shows the occurrences of clinically severe HTN linked with certain anticancer treatments [10].

Tab. 2. Chemotherapy andhHypertension

Chemotherapy Agents	Occurrence	Frequency of Use
Small-Molecule Inhibitors of Tyrosine Kinase		
Sorafenib	18-42	+++
Sunitinib	5-48	+++
Tyrosine Kinase Inhibitor Based on Monoclonal Antibodies		
Bevacizumab	4-4	++

Occurrence

Bevacizumab:

Patients using bevacizumab often get HTN (of any grade), with a reported occurrence range of 4% to 35% in clinical studies. On average, 11% to 18% of individuals had grade 3 HTN. HTN might have appeared at any point during treatment, and some results seem to point to a dose response. In clinical studies, the majority of patients who acquired HTN received sufficient care from antihypertensives and maintained bevacizumab medication. However, up to 1.7% of patients had worsening HTN necessitating hospitalization or stopping bevacizumab medication. Hemorrhages in the central nervous system and hypertensive encephalopathy have been reported as side effects of bevacizumab-induced HTN.

Sorafenib:

In clinical studies, HTN, which affects 17% to 43% of patients, was shown to be a serious side effect of sorafenib treatment. HTN in grade 3 or 4 affected 1.4% to 38% of people. A recent meta-analysis included 4,599 patients on sorafenib showed a total incidence of 23.4% for HTN.

Etiology:

HTN caused by antiangiogenic treatment has an unknown mechanism. The suppression of VEGF, which lowers the formation of nitric oxide in the walls of resistant arteries like arterioles, is likely to be responsible. Because nitric oxide naturally dilates blood vessels, inhibiting its synthesis encourages vasoconstriction, higher peripheral vascular resistance, and higher blood pressure [11].

Diagnosis:

A blood pressure of 140/90 mm Hg is the threshold for HTN according to JNC 7. Based on measured blood pressure measurements, the JNC 7 classification system places people with HTN into several phases. There are three goals to consider while assessing HTN patients: Determine the etiology of HTN. Assess lifestyle to find cardiovascular risk factors or coexisting conditions that might affect prognosis or guide treatment. Determine whether or not HTN-related target organ damage exists.

Treatment

Discontinuing antiangiogenic medication owing to HTN is debatable since grade 3 HTN, in particular, seems to be linked to a greater level of therapeutic response. Since the biological effects of various drugs on angiogenesis vary, there is evidence that certain antihypertensives may be more successful than others when used as an antihypertensive agent. Additionally, since ACE inhibitors may stop proteinuria and the production of plasminogen activator inhibitor-1, using them as first-line treatment may be advantageous. Additionally, in vivo, research has shown that ACE inhibitors may lessen microcirculatory alterations, lessen bradykinin catabolism, and boost endothelial nitric oxide release. Patients on sorafenib should also be aware of drug interactions. Through the cytochrome p450 system, sorafenib is metabolized, mostly by CYP3A4. Amlodipine and nifedipine are recommended when a calcium-channel blocker is given.

CASE 3

Heart failure

The emergence of LVD and/or HF has been linked to the use of several cancer medications. The probability of Cardiomyopathy (CMP) depends on the total dosage, the delivery timing, and the concurrent use of other cardiotoxic medications [12]. The prevalence of LVD linked to certain chemotherapeutic drugs is seen in table 3.

Tab. 3. Treatment with chemotherapy linked to left ventricular dysfunction

Chemotherapy Agents	Occurrence (%)	Frequency of Use
Alkylating Agents		
Cyclophosphamide	8-29	+++
Ifosfamide	18	+++
Anthra Cyclones		
Doxorubicin	3-27	+++
Epirubicin	0.8-3.3	++
Idarubicin	7-19	+
Anti-Microtubule Agents		
Docetaxel	2.3-8	++
Anti-Metabolites		
Clofarabine	27	+
Tyrosine Kinase Inhibitors Derived from Monoclonal Antibodies		
Bevacizumab	18-3	++
Trastuzumab	3-29	++
Small-Molecule Inhibitors of Tyrosine Kinase		
Imatinib mesylate	0.5-16	+
Dasatinib	2-4	++
Lapatinib	16-22	+
Sunitinib	27.11	+++
Proteasome Inhibitor		
Bortezomib	2-4	++

Occurrence

Anthracyclines:

Acute, early-onset chronic progressive, and late-onset chronic progressive anthracycline-induced cardiotoxicity have all been classified. Initial cardiotoxicity, which appears as an initial, transitory reduction in cardiac contractility that is often reversible, arises immediately following the infusion of anthracycline in 1% of individuals. The early-onset chronic progressive form manifests during therapy or in the first-year post-treatment in 1.6% to 2.1% of patients [13].

Proteasome inhibitor

Bortezomib:

In a major clinical study, bortezomib or high-dose dexamethasone was administered to 669 individuals with multiple myeloma. Comparatively to individuals receiving dexamethasone, 15% of patients receiving bortezomib had cardiac problems following therapy. Between 4% and 5% of individuals receiving dexamethasone and 5% of those receiving bortezomib had HF episodes. Each of the therapy groups included 2% of individuals who also had HF [14].

Tyrosine kinase inhibitors based on antibodies

Bevacizumab:

The range of HF prevalence is 1.7% to 3%. The prescription instructions state that 24 of the 1,459 individuals (1.7%) who received bevacizumab during clinical trials had HF. In 2 phase 3 clinical trials including patients with metastatic breast cancer, the bevacizumab-treated groups had a 2.2% to 3% chance of grade 3 to 4 heart failure or Cardiac Myopathy (CMP).

Small molecule tyrosine kinase inhibitors

Dasatinib:

Dasatinib treatment is associated with an occurrence of HF that ranged from 2% to 4%. HF or cardiac dysfunction occurred in 2% of leukemia patients across all dasatinib investigations, with grade 3 or 4 dysfunctions occurring in 1% of these individuals. Up to 2% of patients had HF/LVD with a grade 3 or 4 occurrence.

Lapatinib:

The cardiac safety of lapatinib was investigated in recent pooled research involving 3,689 participants in phase I through 3 clinical studies. Asymptomatic (grade 3 or 4) or symptomatic cardiac episodes was classified as such. 60 (1.6%) of the 3,689 patients had a cardiac event. 53 individuals (1.4%) had asymptomatic cardiac events described, whereas 7 patients (0.2%) had symptomatic events [15].

Sunitinib:

In early treatment studies, 4% to 11% of individuals with metastatic renal cell carcinoma and gastrointestinal stromal tumors were found to have LVD. 2 retrospective evaluations assessing the cardiotoxicity of sunitinib were just published. Coronary artery disease was the only substantial risk factor linked to the onset of HF. The average time it took for HF to develop ranged from 22 days to 27 weeks. Medical treatment for sunitinib-induced HF seems to work effectively, however, CMP may not be fully reversible [16].

Etiology

Anthracyclines:

Several theories attempt to explain how anthracyclines cause cardiotoxicity, but the predominant theory is free radical production, which is widely acknowledged. Doxorubicin's interaction with topoisomerase II beta has recently been theorized as a potential mechanism for cardiotoxicity.

Cyclophosphamide:

Cyclophosphamide cardiotoxicity's exact mechanism is unclear. Cyclophosphamide is thought to directly harm endothelial cells before toxic metabolites extravasate and cause harm to cardiomyocytes, interstitial bleeding, and edema. Additionally, intracapillary micro emboli may form, harming the myocardium through the ischemic stroke. Another suggested mechanism of cardiotoxicity is myocardial ischemia brought on by coronary vasospasm.

Trastuzumab and lapatinib:

It may control mitochondrial integrity by attaching to ErbB2, which would impair contractile activity and deplete ATP. Drug-drug interactions and cardiomyocyte damage caused by the immune system are 2 more possibilities [17].

Bortezomib:

A decline in proteasome activity associated with aging has also been linked to cardiovascular disease vulnerability. As a result, the ubiquitin-proteasome system is activated in individuals who already have subclinical CMP, which puts them at risk for developing bortezomib cardiotoxicity.

Diagnosis:

HF is clinically diagnosed by a combination of the patient's clinical history, physical exam, and diagnostic techniques.

Monitoring:

Regular heart function monitoring is crucial throughout treatment to identify cardiac dysfunction in individuals receiving chemotherapy. It is necessary to evaluate LVEF at a baseline for comparison, and it is advised to compare serial examinations using the same methods. The value of serial LVEF testing was first shown in clinical practice.

Since it is the most sensitive and specific method of diagnosis, endomyocardial biopsy continues to be the gold standard; nonetheless, the procedure's invasiveness restricts its application. The noninvasive nature of MUGA scans makes them a desirable choice for regular clinical monitoring; however, the only information that can be detected by MUGA scans is reductions in LVEF. Additionally, it lacks sensitivity for early toxicity detection. Contrarily, echocardiography, which is likewise noninvasive, may detect pericardial and valvular illness in addition to systolic and diastolic dysfunction. Before alterations in LVEF become obvious, biochemical indicators may potentially suggest myocardial damage [18].

Prevention:

Given that a patient's cumulative dose is a significant risk factor for CMP caused by anthracycline, reducing the cumulative dose received by the patient throughout their lifetime is an important prophylactic approach. Altering the administration of anthracyclines, using anthracycline analogs, or liposomal anthracyclines, and adding cardio protectants to anthracycline treatment, have all been shown to reduce cardiotoxicity.

Treatment

There are no established HF recommendations for cancer patients at this time. Improved survival, slowed disease progression, and symptom relief is the goals of treatment for stages B, C, and D. These drugs have been found to improve survival by reversing remodeling. Additional treatments, such as diuretics, digoxin, or aldosterone antagonists, are often necessary for patients with advanced HF [19].

Patients with end-stage HF who continue to have resting symptoms after maximum pharmacological treatment may be candidates for synchronized pacing, a ventricular assist device, or a heart transplant if there is no indication of cancer recurrence. Myocyte death is a hallmark of anthracycline-induced cardiotoxicity, thus even though patients may have a clinical improvement in response to therapy, the underlying etiology seldom resolves.

Patients with anthracycline-induced CMP may benefit from using ACE inhibitors. Enalapril was shown to reduce the risk of LVEF decrease and cardiac events in cancer patients following high-dose chemotherapy compared to the control group. In some people, ACE inhibitors may slow the progression of heart dysfunction, but this is not the case for everyone. More human studies are needed to ascertain whether preventing acute toxicity mitigates the potential for early or late cardiotoxicity. Only four case studies have looked at the effectiveness of beta-blockers for anthracycline-induced CMP. Carvedilol, unlike other beta-blockers, has been demonstrated to have antioxidant capabilities, which might make it a useful treatment option for treating anthracycline-induced CMP. Patients receiving anthracycline treatment had their systolic and diastolic functions better preserved with prophylactic carvedilol usage, compared to placebo.

When HF becomes clinically serious, it is usually advised to stop trastuzumab treatment. However, after discontinuing trastuzumab, individuals who have cardiotoxicity often regain full cardiac function within 1.5 months. Patients receiving trastuzumab treatment have recommendations recommended for their care based on their physical state and Left Ventricular Ejection Fraction (LVEF) from Memorial Sloan-Kettering Cancer Center [20].

CASE 4

Bradycardia

In cancer patients, a variety of circumstances can lead to bradycardia and heart block. The cardiac conduction system may be impacted by fibrosis brought on by aging or radiation therapy, as well as diseases like amyloidosis and primary cardiac tumors. Additionally, paclitaxel and thalidomide are the 2 most clinically relevant chemotherapeutic drugs that have been linked to bradycardia and heart block in cancer patients [21]. Table 4 lists the instances of bradycardia linked to particular chemotherapeutic drugs.

Tab. 4. Bradycardia and chemotherapy

Chemotherapy Agents	Occurrence	Frequency of Use
Antimicrobe Tubule Agent		
Paclitaxel	0.12-54	+
Angiogenesis Inhibitor		
Thalidomide	0.15-56	+

Occurrence

Paclitaxel:

In early phase I clinical studies, a high prevalence of significant hypersensitivity events led to the implementation of continuous monitoring of patients receiving paclitaxel therapy; it was around this time that cardiac toxicity was first identified. The occurrence of cardiac events led to the exclusion of participants with preexisting cardiac conditions or those using medications that might potentially disrupt normal cardiac conduction from further study. Asymptomatic, reversible bradycardia has been seen in patients receiving paclitaxel, which has been linked to cardiac arrhythmias. There is a wide range in the published literature for the reported frequency of bradycardia due to paclitaxel, from 0.1% to 31%.

Thalidomide:

The package insert for thalidomide does not include information on the occurrence of bradycardia when taking the drug. The adverse event reporting rate in post-marketing monitoring studies was 0.12%. Similarly, just 2% of participants in a phase III study comparing thalidomide with dexamethasone to dexamethasone alone in newly diagnosed multiple myeloma patients had sinus bradycardia [22].

Etiology

Paclitaxel:

Cremophor EL, the carrier used to create paclitaxel, may also contribute to cardiac side effects. Cremophor EL has been shown to cause histamine to be released in situations of hypersensitivity responses. Histamine receptors in cardiac tissue are stimulated, leading to increased myocardial oxygen demand, coronary vasoconstriction, and chronotropic effects. Stimulation of H1 receptors has been shown to cause ventricular arrhythmias, myocardial cell damage, and a lengthening of atrioventricular conduction in animal experiments.

Diagnosis:

The term bradycardia is typically used for a heart rate of 60 beats per minute or below. Although many people have no symptoms at all when their heart rate is below 50 beats per minute, some patients may also experience fatigue, physical activity limits, syncope, or dizziness. Holter monitoring, Electrocardiograms (ECGs), and tests for underlying illnesses such thyroid conditions or imbalances in electrolytes are among the diagnostic methods used to identify the kind of bradycardia.

Treatment

Paclitaxel:

Although bradycardia brought on by the use of paclitaxel generally has little clinical importance, some individuals have needed pacemakers installed. Except for individuals with severe conduction problems, continuous cardiac monitoring is rarely necessary. In any event, given that many of these instances are asymptomatic, bradycardia by itself does not seem to be a reason to stop taking paclitaxel [23].

Thalidomide:

Whether the patient is exhibiting symptoms will determine how bradycardia is treated. Asymptomatic patients often do not need treatment, although cautious monitoring is always advised. In some circumstances, thalidomide dosage needs to be decreased daily. Thalidomide therapy should be stopped to manage symp-

tomatic bradycardia. When there are no other treatment options for individuals with multiple myeloma whose illness responds to thalidomide therapy, some patients have pacemakers placed so they may continue taking thalidomide.

CASE 5

Ischemia

A Patient with cancer often develops chest discomfort, which necessitates testing for myocardial ischemia. Numerous cancer therapies are associated with an increased risk of Acute Coronary Syndrome (ACS) and/or coronary artery disease. Table 5 highlights chemotherapeutic substances linked to the onset of myocardial ischemia/infarction.

Tab. 5. Ischemia associated with chemotherapy

Chemotherapy Agents	Occurrence (%)	Frequency of Use
Antimetabolites Capecitabine	3-10	+++
Fluorouracil	1-67	+++
Monoclonal Antibody-Based Tyrosine Kinase Inhibitor		
Bevacizumab	0.7-1.5	++
Anti-Microtubule Agents		
Paclitaxel	<1-4	+++
Docetaxel	1.8	++
Small Molecule Tyrosine Kinase Inhibitors		
Erlotinib	2.3	+++
Sorafenib	2.8-2	+++

Occurrence

Antimetabolites

Fluorouracil:

Chest discomfort resembling angina is the most frequent sign of 5-fluorouracil (5-FU) cardiotoxicity. The prevalence of cardiotoxicity linked to 5-FU ranges from 1% to 68%. Cardiac episodes may last up to 48 hours and often happen 2 days to 5 days after treatment begins. Only 43% of patients had elevated blood cardiac markers, but 68% of patients reported ischemic Electrocardiogram (ECG) abnormalities. An estimate of the total mortality ranges from 2.2% to 13%.

Capecitabine:

Uncertainty persists about the prevalence and risk factors of cardiotoxicity brought on by capecitabine. 5.5% of 644 individuals in one prospective analysis had capecitabine-related cardiotoxicity. The occurrence of cardiotoxicity varies from 3% to 9% based on the 4 published retrospective studies. Many instances included ECG alterations, such as ST-segment elevation; nevertheless, when serum cardiac markers were examined, all but one showed normal results. Both the coronary angiography and the echocardiogram were normal. Since it was absent in some patients but present in others, previous heart illness was not a constant risk factor [24].

Antimicrotubular agents

Paclitaxel:

Myocardial ischemia and infarction cases connected to the use of paclitaxel have been documented. A MI occurred in 0.5% of the 198 patients who had paclitaxel treatment for ovarian cancer. Up to 14 days following the administration of paclitaxel, several occurrences took place. The majority of cases showed that patients were aware of known cardiac risk factors, such excessive blood pressure and coronary artery disease.

Monoclonal antibody-based tyrosine kinase inhibitors

Bevacizumab:

Compared to patients receiving chemotherapy alone, people using bevacizumab have Arterial Thrombotic Events (ATEs) more often. The occurrence of major ATEs was 1.8% in current observational research including 1,953 patients who received bevacizumab along with chemotherapy. Of the patients having an ATE, 11 individuals (0.6%) suffered a MI. Events did not seem to be related to exposure level or cumulative exposure. Risk variables found include age >65 and a history of past ATEs.

Small molecule tyrosine kinase inhibitors

Sorafenib:

In clinical studies, myocardial ischemia has occurred in around 3% of people on sorafenib. In an unreported clinical study, 2.7% of hepatocellular carcinoma patients receiving sorafenib had MI/ischemia compared to 1.3% of patients receiving a placebo. Similarly, sorafenib was associated with a higher rate of MI/ischemia (3% vs. 1%) in patients receiving treatment for renal cell carcinoma when compared to placebo.

Etiology

Fluorouracil and capecitabine:

The theory of coronary vasospasm was supported by a study in which elevated levels of endothelin-1 were discovered in some patients. Alternative mechanisms have thus been created, such as autoimmune reactions, coagulation system interactions, and direct toxicity on the heart. Citrate buildup in cardiac cells has been hypothesized to be the cause in animal studies. The Krebs cycle is hampered by the synthesis of fluoroacetate, which is the cause of this buildup. Fluor acetaldehyde, a breakdown byproduct of parenteral 5-FU preparations, is used to make fluoroacetate. Last but not least, inflammatory lesions that resemble toxic myocarditis may develop as a consequence of myocardial and endothelial cell death.

Paclitaxel:

Paclitaxel-induced myocardial ischemia is thought to have a complex etiology that may involve both concomitant drug usage and preexisting heart disease. Additionally, the cardiac toxicity of paclitaxel may be caused by the Cremophor EL vehicle in which it is manufactured; the mechanism is probably caused by the drug's activation of histamine release.

Diagnosis:

The clinical manifestation of the patient, changes in the ECG, and increases in cardiac enzymes are used to make the diagnosis of ACS. Acute myocardial infarction is now the appropriate phrase to use when there is evidence of myocardial necrosis in a clinical situation suggestive of myocardial ischemia.

Treatment:

The mainstays of ACS therapy include antiplatelet, anticoagulant, and percutaneous coronary intervention. Some cancer patients experience problems because of thrombocytopenia or recent surgery. Patients who have chest discomfort should stop taking 5-FU or capecitabine. A work-up for ischemia and antianginal medication should also be started. These trials' findings, meanwhile, did not consistently point to an advantage. Retesting patients who experienced cardiotoxicity with 5-FU or capecitabine in the past is a contentious issue. These drugs should only be administered to patients who have run out of other therapeutic alternatives, and only under close supervision. Additionally, it may be wise to keep a close eye on individuals who have 5-FU or capecitabine-induced cardiotoxicity risk factors [25].

CASE 6

QT Prolongation

QT interval prolongation is an anomaly in the heart's electrical activity that puts a person at risk for ventricular arrhythmia. Because 16% to 36% of cancer patients have aberrant baseline ECGs, they may be more susceptible to QT prolongation than other groups of patients. In addition, nausea, vomiting, diarrhea, and reduced oral intake are common in cancer patients. These side effects might cause electrolyte imbalances, which increase the likelihood of QT prolongation in the patient [26]. The frequency of QT prolongation linked to certain chemotherapeutic drugs is shown in table 6 in bold.

Tab. 6. QT Prolongation with chemotherapy

Chemotherapy Agents	Occurrence	Frequency of Use
Inhibitor of Histone Deacetylase		
Vorinostat	3.5-7	+
Small Molecule Tyrosine Kinase Inhibitors		
Dasatinib	<1-4	++
Nilotinib	1-11	+
Miscellaneous		
Arsenic trioxide	25-94	+

Occurrence

Dasatinib:

A total of 9 patients (1.8%) of the safety group receiving dasatinib for chronic myeloid leukemia had QT prolongation was noted as an adverse event, and 7 more patients (1.4%) had an ECG that showed 500 ms of QTc prolongation. Additionally, according to a briefing document provided to the Oncology Drug Advisory Committee, QT prolongation affects 2% to 3% of dasatinib-using patients (FDA websites). A 500-ms QTC interval was experienced by 3 patients (1%) and was documented as an adverse event in 9 individuals.

Etiology:

The cause of QT prolongation brought on by the drugs described in the paragraph above is still a mystery. It is now known that drugs block the delayed rectifier potassium current, which is at least partially what causes their pro-arrhythmic impact when talking about drug-induced QT prolongation. Additionally, if underlying long QT syndrome is present, 1 or more risk factors may cause a considerable QT interval lengthening.

Diagnosis:

An electrocardiographic diagnostic is QT prolongation. In the medical literature, QT prolongation is defined differently, and it is still unknown whether specific levels put patients at risk for cardiac problems. Men's and women's QTc intervals are regarded as protracted if they are longer than 450 ms and 470 ms, respectively and normal if they are 440 ms or less. Concern about the possible danger of an arrhythmia is raised by variations of 500 milliseconds following the administration of a medication or 60 milliseconds from the baseline. QT interval lengthening may be caused by acquired and congenital causes [27].

Treatment:

Every anticancer medication under consideration has recommended baseline and recurring electrocardiogram monitoring, and possible dose modifications and treatment termination in the event of QT prolongation. All of these medications should be administered with caution to patients who have any of the risk factors for QT prolongation, congenital long QT syndrome, and cumulative high-dose anthracycline therapy. Before beginning these drugs, it is also advisable to address hypokalemia and hypomagnesemia. The risk of arrhythmias should be discussed with patients before therapy, and they should be encouraged to report any palpitations or other cardiac symptoms. Another alternative for patients is isoproterenol, which is helpful when temporary pacing is not available or while getting ready to install a transvenous catheter. It should be titrated to a heart rate of 90 beats per minute.

CONCLUSION

Cardiotoxicity caused by cancer treatments has been the subject of much research in the past, but there is still more that can be

done. Medical knowledge is always changing, so it is important to analyze the findings carefully. A better understanding of the long-term effects of radiation and contemporary systemic therapies on vital cardiac structures is required, as well as any potential interactions between different treatment methods. This information can help cancer survivors live longer and have a greater quality of life with less treatment-related morbidity from other diseases. To choose a main therapy and ensure proper follow-up following cancer treatment, prediction models that account for the complete range of late effects are required.

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