ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

AJPBR

Indexed by:

ROAD Crossref Universal Impact Factor IMPACT FACTOR SEARCH

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 13 Issue 2
MAY-AUG. 2024

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VENTRICULAR ARRHYTHMIA IN CANCER PATIENTS: UNDERSTANDING THE CAUSES AND IMPLEMENTING EFFECTIVE TREATMENT APPROACHES

Ergashov B.B.
Bukhara State Medical Institute, Bukhara, Uzbekistan.

Abstract. Cardiovascular disease and cancer are the top causes of illness and death around the world. Despite the progress in cancer treatment, ventricular arrhythmias (VA) remain a significant cardiovascular complication caused by traditional and new cancer treatments. Understanding this issue is crucial for optimizing patient care. This review will discuss ventricular conduction (QRS) and repolarization abnormalities (QTc prolongation) associated with cancer therapies, as well as strategies for identifying, preventing, and managing cancer-treatment-induced vascular issues.

Keywords: cancer, oncology, cardio-oncology, arrhythmia, corrected QT interval.

Introduction. Cardiovascular diseases and cancer are a significant cause of illness and death worldwide. Recent advancements in cancer treatment have improved outcomes, resulting in more people surviving cancer. However, there has been an alarming increase in cardiovascular diseases, such as ventricular arrhythmias (VA), among cancer patients. It is challenging to determine the arrhythmogenicity of cancer therapies because the standard testing protocols used for healthy individuals before drug approval cannot be applied to chemotherapeutic agents[1].

Cancer treatment-associated arrhythmia is a form of cardiotoxicity that is increasingly relevant and described in the literature, but poorly understood and characterized because of the heterogeneity of malignancies, multitude of cancer treatments, pre-existing cardiovascular risk factors, and unclear arrhythmogenic mechanisms. The increasing age of the population with cancer, overlapping risk factors (hypertension, diabetes, hyperlipidemia, inflammation, and obesity), and history of cardiovascular diseases can predispose certain patients to a higher risk of developing arrhythmias during and after cancer treatment. In a recent evaluation of post-marketing safety communications for 125 cancer therapeutics approved by the Food and Drug Administration (FDA), arrhythmias were the most common reason for cardiovascular disease warnings (23.5%).

Acute cardiotoxicity during treatment may prevent the use of potentially life-saving cancer therapies. Long-term survival and quality of life can be affected by chronic toxicities after treatment. Arrhythmic cardiotoxicity can occur due to direct effects of the drug disrupting specific molecular pathways leading to arrhythmias, or as a result of damage to the cardiac structure from ischemia, inflammation, or radiation therapy, with ventricular arrhythmias (VA) as a resulting phenomenon. The mechanisms underlying arrhythmias in cancer patients are complex and involve both cancer and non-cancer treatment adverse effects, as well as electrolyte

disturbances[2].

To illustrate the importance of understanding the causes of arrhythmogenicity related to the wide spectrum of cancer treatments, prior scientific statements and guidelines have been published. In this review, we will describe the known associations of traditional and novel cancer treatment agents with ventricular conduction (QRS) abnormalities.

Next, we will review specific drug classes associated with QT prolongation and ventricular arrhythmia. Finally, we will discuss known approaches and strategies for identifying and preventing cancer treatment-induced ventricular arrhythmia[3].

Ventricular Repolarization Abnormality (QT Prolongation): The QT interval, which represents ventricular repolarization, is the main indicator used to assess the arrhythmic risk of a drug. When cardiac repolarization is prolonged, it is reflected in ECGs as a prolonged QT interval that is corrected for heart rate using various methods. Prolonged QT interval increases the risk of a specific type of ventricular arrhythmia called torsades de pointes (TdP), which can lead to symptoms, sudden cardiac arrest, and death. Due to this safety concern, all drugs undergo preclinical assessment in healthy volunteers to evaluate the risk of TdP as an unintended effect[4]. However, in cancer treatments, these safety studies are conducted in cancer patients with normal corrected QTc intervals (QTc) and normal electrolyte values. A recent review of 205 anticancer drugs found that only around 10% of these drugs (22 out of 205) had undergone thorough QT/QTc assessment. QTc prolongation is quite common in cancer patients receiving chemotherapy, with a reported incidence of up to 30%. Cancer patients have been found to be more susceptible to QTc prolongation compared to the general population. Possible reasons include direct effects of cancer treatments on cardiac repolarization through potassium channels like the human gene (KCNH2) and the rapid component of the delayed rectifier potassium current (IKr). Other pathways, such as inhibition of phosphoinositide 3-kinases or upstream kinases, have also been reported to cause prolonged QTc. Moreover, confounding factors such as electrolyte imbalances, exacerbated by gastrointestinal side effects like nausea, vomiting, and diarrhea, as well as simultaneous use of medications like painkillers, antibiotics, antifungals, antidepressants, and antiemetics, can further prolong the QTc interval[5].

It is crucial to thoroughly evaluate the QT interval before and during cancer treatment to ensure that potentially beneficial therapy is not withheld due to exaggerated concerns about arrhythmia risks from QTc prolongation. It is important to use accurate QTc calculation methods and to be aware of the strengths and weaknesses of different formulae[6]. Borad et al. conducted a study on cancer patients participating in clinical trials and found that using different QTc formulae, such as Bazett's and Fridericia's, led to varying rates of ineligibility, ranging from 3.1% to 17.7%. Using Fridericia's formula resulted in a lower ineligibility rate of 3.9% compared to 10.8% with Bazett's formula. Other studies have also shown that Bazett's formula tends to overestimate QTc interval, while Fridericia's formula

provides more accurate predictions. Therefore, it is recommended to use the Fridericia correction method for QTc calculation in cancer patients. Additionally, it is important to interpret the QTc interval carefully when the heart rate is irregular or in the presence of a pre-existing bundle branch block or pacemaker rhythm[7].

Ventricular Conduction Abnormalities: QRS Fragmentation and Prolongation. The QRS duration corresponds to ventricular depolarization. Monitoring QRS duration is routinely used in caring for patients at risk for developing arrhythmias and heart failure. Electrical depolarization abnormalities, defined as QRS duration of ≥120 ms, can be a result of chronic or acute conduction system disease, myocyte-cell injury, cardiac tissue inflammation, and interstitial fibrosis. QRS prolongation, both before the initiation of chemotherapy and during treatment, has been shown to be associated with an increased risk for cardiac dysfunction, ventricular arrhythmias, and major cardiovascular events. Therefore, a prolonged QRS can be used to recognize subclinical cardiac damage and possibly trigger cardiac risk stratification of patients on chemotherapy, impacting acute and long-term outcomes[7].

QRS fragmentation (fQRS) is a marker of abnormal ventricular depolarization. It can occur due to changes in the electrical signals traveling through the myocardium, which can distort the QRS waveform. This has been observed in patients with myocardial scarring after myocardial infarction (MI) and is considered a potential non-invasive marker for identifying patients at risk for sudden cardiac death (SCD). The prevalence of fQRS ranges from 1% to 30% in the general population but is much higher in cancer patients after undergoing chemotherapy (24). Myocardial fibrosis is a known adverse effect of cancer therapy, and chemotherapies can trigger apoptosis or necrotic myocyte death. Studies have highlighted the importance of fQRS in recognizing chemotherapy-related cardiotoxicities, even before the development of cardiac symptoms or echocardiographic abnormalities[8].

Ventricular arrhythmias can occur in cancer patients due to metabolic changes at a cellular level caused by the cancer itself and its treatments. According to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0), there are four grades of severity for cardiac events: Grade 1 (asymptomatic, intervention not needed), Grade 2 (non-urgent medical intervention required), Grade 3 (urgent medical intervention needed), and Grade 4 (life-threatening consequences, haemodynamic compromise). The QTc interval is often used as a measure for drug-induced ventricular arrhythmia risk, although it's not perfect[9].

Certain treatments, like Bruton tyrosine kinase inhibitors (BTKi) and chimeric antigen receptor T-cell (CAR-T) therapy, have been linked to ventricular arrhythmias without concomitant QT prolongation. This has been attributed to changes in cardiac sarcoplasmic reticulum Ca2+ homeostasis associated with cardiac ryanodine receptor-calmodulin-dependent protein kinase pathways. While the potential complications of ventricular arrhythmias and sudden cardiac arrest are serious, actual arrhythmic events associated with QTc prolongation are rare.VAs, such as premature

ventricular contractions (PVCs) and non-sustained ventricular tachycardia (NSVT), have been reported to have higher prevalence in patients with cancer than in those without cancer (8.0% versus 0%).30 This may plausibly be attributed to factors, such as heightened clinical surveillance, the inflammatory milieu of malignancy, as well as the use of cardiotoxic chemotherapeutic agents. Among 120 patients with lung, colon and pancreatic cancers, NSVT and PVCs were both significant independent predictors of mortality during long-term follow-up.

The occurrence of ventricular arrhythmias (both low-grade, such as premature ventricular contractions or brief non-sustained ventricular tachycardia episodes, and malignant ventricular tachycardia) and sudden cardiac death in patients with cardiac tumors has been reported in several published case reports and case series. It's important to note that cardiac tumors are a rare cause of arrhythmias, and the true prevalence of primary cardiac tumors causing sudden cardiac death is unknown and may be underestimated, as post-mortem analysis is not performed on all patients[9]. The morphology of premature ventricular contractions reflects the chamber of origin; a right bundle branch block pattern is seen in 80% of cases (indicating left-ventricular origin), and a left bundle branch block is present in 20% of cases (indicating right-ventricular origin). Possible mechanisms include tissue compression, mass effect (involving cardiac cavity, coronary vasculature, or obstruction of heart valves and outflow tracts), extensive bleeding into the lesion leading to tamponade, scarring and creation of re-entrant pathways producing ventricular tachycardia, and asynchronous refractoriness within the abnormal tissue leading to electrical instability[10].

Cancer Treatments Associated with QTc Prolongation and Ventricular Arrhythmia: Arsenic Trioxide is used to treat otherwise fatal acute promyelocytic leukaemia (APL) but has been found to cause prolongation of the QT interval (in 30–90% of cases) and Torsades de Pointes (TdP) at therapeutic doses. Mild prolongation of the QT interval (440–500 ms) is commonly observed and should not prevent the use of arsenic trioxide. It is recommended to perform electrocardiograms (ECGs) at baseline and during therapy (weekly monitoring) along with close monitoring of electrolyte levels. If the QT interval is >500 ms, aggressive correction of abnormal serum potassium, magnesium, calcium, and creatinine levels should be initiated, and alternative treatment regimens should be considered if significant QT prolongation persists[11]. For patients experiencing clinical symptoms (such as syncope, palpitations, or irregular heartbeat), hospitalization for cardiac monitoring should be considered even with a QT interval <500 ms, with a plan to resume arsenic trioxide therapy only after symptom resolution, QTc <460 ms, and electrolyte correction. Alpha lipoic acid and mexiletine may help minimize arsenic-induced QT prolongation and recurrent TdP, although further research is needed to determine the efficacy and safety of this approach[12].

Anthracyclines (AC) are highly effective and commonly used chemotherapy drugs. It has been reported that even within a safe dosage range, patients treated with anthracyclines may experience QT prolongation and TdP weeks to years after

treatment. Interestingly, the risk of QTc prolongation increases with subsequent AC cycles and can lead to ventricular arrhythmias[13]. Both electrocardiographic changes (ST-T segment changes, QRS voltage lowering, T-wave flattening, QTc interval prolongation) and ventricular arrhythmias have been reported in approximately 30-66% of patients, with occurrences even during the first cycle of therapy. A fragmented QRS complex (fQRS) has been observed in 27% of breast cancer patients and 29% of large B-cell lymphoma patients treated with AC. The prevalence of ventricular arrhythmias in AC-related cardiomyopathy has been found to be similar to non-cancer-related cardiomyopathy. Dexrazoxane, an FDA-approved drug for patients with metastatic breast cancer (who have received a cumulative AC dosage above a threshold of 300 mg/m2 for doxorubicin or >550 mg/m2 for epirubicin), may be used to protect the heart from anthracycline-induced QT prolongation[14].

Anthracyclines (AC) are highly effective and commonly used chemotherapy drugs. They can cause QT prolongation and Torsades de Pointes (TdP) in patients, even when administered within a safe dose range, and symptoms can appear weeks to years after treatment. Interestingly, the risk of QT prolongation increases with each subsequent AC cycle and can lead to ventricular arrhythmias. Electrocardiographic changes (such as ST-T segment changes, QRS voltage lowering, T-wave flattening, and QT prolongation) and ventricular arrhythmias have been reported in about 30-66% of patients, with some experiencing symptoms during the first cycle of therapy. In patients treated with AC for breast cancer and large B-cell lymphoma, fragmented QRS complexes (fQRS) have been reported in 27% and 29% of cases, respectively. The prevalence of ventricular arrhythmias in AC-induced cardiomyopathy is similar to that in non-cancer-related cardiomyopathy. Dexrazoxane, an FDA-approved drug for patients with metastatic breast cancer, can be used to protect the heart from anthracycline-induced QT prolongation in cases where cumulative AC dosages exceed certain thresholds. For doxorubicin, the threshold is 300 mg/m2, and for epirubicin, it's 550 mg/m2[15].

In this review, we have summarized the literature on ventricular conduction and repolarization abnormalities in cancer patients. Ventricular arrhythmias, especially premature ventricular contractions (PVCs) and other abnormalities such as QTc prolongation, are common but can often be managed without significant treatment interruptions. This can be achieved through adjustments to surrounding factors, such as correcting electrolyte imbalances and carefully reviewing concurrently administered medications [16].

Conclusion. Cancer patients have several factors that can contribute to or worsen various ventricular arrhythmias, and certain cancer treatments may significantly increase the risk of these conditions. Being aware of the chemotherapies, modifiable factors, high-risk features, and underlying mechanisms that can predispose patients to these arrhythmias is crucial. Attention to risk factors and underlying health conditions can help in prevention and risk reduction.

However, there is still much unknown about the overall incidence,

mechanisms, and optimal methods for reducing the risk of cancer treatment-related ventricular arrhythmias. There is an urgent need for more basic, translational, and innovative research utilizing digital technologies. This should involve collaboration between oncologists and cardiologists to develop evidence-based management strategies for this unique and vulnerable population.

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