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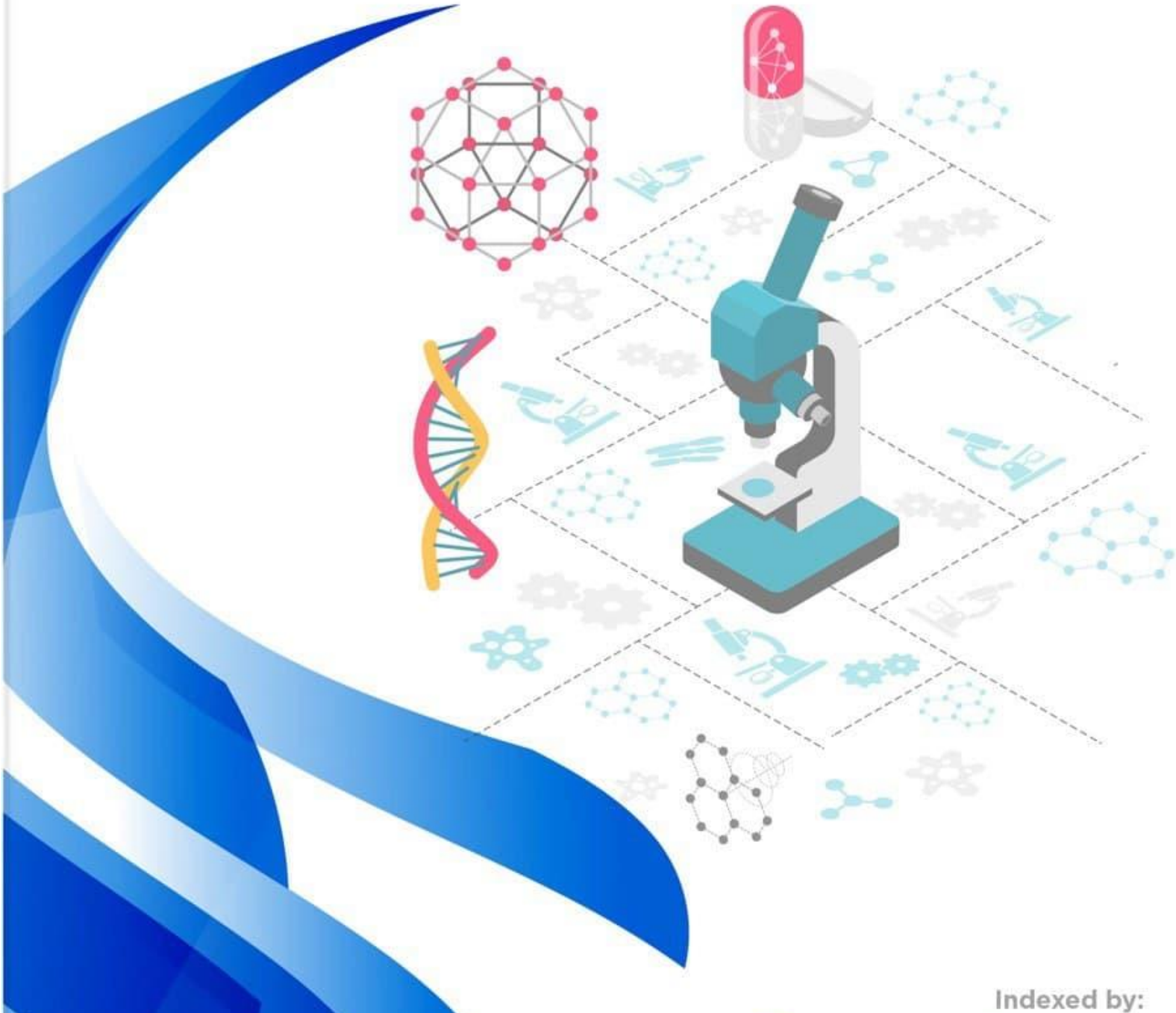

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EPIDEMIOLOGY, RISK FACTORS AND MANAGEMENT OF CARDIAC ARRHYTHMIAS IN ONCOLOGY PATIENTS

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Abstract. The purpose of this review is to provide an update on the epidemiology, risk factors, and management of cardiac arrhythmias in oncological patients, in the context of the new European Society of Cardiology 2022 guidelines on cardio-oncology. It has been found that some chemotherapeutics have pro-arrhythmic activity, leading to the induction of both atrial and ventricular arrhythmias. Recent studies have reported on the cardiotoxic activity of promising therapies such as BRAF and MEK inhibitors, as well as CAR-T therapy. Risk factors for arrhythmias in oncological patients overlap with those of cardiovascular diseases, but certain groups of anticancer drugs increase the risk of cardiotoxicity. It is crucial to be aware of the risks associated with oncological treatment and to know how to act in case of cardiotoxicity.

Keywords: Arrhythmia, Cardio-oncology, Cardiotoxicity, Cardiovascular disease

Introduction. Cardiovascular diseases (CVD) and cancer are the two leading causes of death worldwide, and their prevalence is constantly increasing. In Europe, cancer accounted for 1,345,680 deaths in 2014, and over 1,409,700 deaths in 2019. On the other hand, CVD causes over 4,000,000 deaths in Europe per year, which accounts for 45% of overall deaths. In August 2022, the European Society of Cardiology (ESC) presented the first-ever official guidelines on cardio-oncology. The new guidelines aim to standardize the management and facilitate the care of cancer patients who are exposed to the heart-related effects of anti-cancer treatment. With the trend of increasing life expectancy, the number of elderly people in the population at higher risk of developing cancer and CVD, such as arrhythmias, is also rising. The most common arrhythmia observed in cancer patients, as in those without diagnosed cancer, is atrial fibrillation (AF). Other types, such as QT-prolongation, ventricular arrhythmias (VA), and bradyarrhythmias, can also appear, but less frequently.

Epidemiology. The occurrence of arrhythmias in patients with cancer varies depending on the type of cancer, the treatment received, the patient's characteristics, and any risk factors involved.In the general population, the overall incidence of atrial fibrillation (AF) ranges from 1 to 2%. However, among cancer patients, this figure increases to between 5% and 16%, depending on the specific risk factors and type of cancer [3,4].The incidence of ventricular arrhythmias (VAs) is lower compared to atrial arrhythmias. However, the potential complications following a cardiac arrest

are more severe. Certain groups of medications are known to prolong the QT interval, including antiarrhythmics, antidepressants, antifungals, and antiemetics. Other risk factors that increase the likelihood of VAs in cancer patients are electrolyte imbalances and inappropriately adjusted doses of drugs that prolong the QT interval and are cleared by the kidneys or liver [3].The prevalence of arrhythmias in oncological patients differs, depending on the cancer type, oncological treatment, patient's characteristics and risk factors.

Please take note of the following text:The overall occurrence of AF in the general population ranges from 1 to 2%. Among cancer patients, it can be as high as 5% to 16%, depending on the risk factors and type of cancer [3,4]. The incidence of VAs is lower compared to atrial arrhythmias, but the potential complications after a possible cardiac arrest are more severe. Several types of medications, such as antiarrhythmics, antidepressants, antifungals, or antiemetics, are known to prolong QT intervals. Other risk factors for VAs in cancer patients include electrolyte imbalances and improperly adjusted doses of medications that prolong the QT interval due to clearance by the kidneys or liver [3]. Bradycardia is identified as a heart rate below 60 beats per minute and is rare among cancer patients. Most episodes of bradyarrhythmia are asymptomatic, and there is generally little need to adjust medication doses or intervene. The most well-known group of chemotherapeutic agents that may cause bradycardia are anaplastic lymphoma kinase (ALK) inhibitors, such as crizotinib or ceritinib, commonly used in the treatment of non-small cell lung cancer (NSCLC) [4]. A retrospective analysis of 153 patients was conducted, including those who had at least one pretreatment heart rate (HR) measurement and were subsequently given crizotinib for advanced NSCLC therapy. A total of 41.9% of patients experienced at least one documented episode of sinus bradycardia (SB). The average maximum decrease in HR was 30.0 bpm, which was higher than in patients who did not experience sinus bradycardia, where the average maximum decrease in HR was 21.4 bpm; 5.9% of the 44 patients experienced the lowest HR below 45 bpm. The majority of patients (75.3%) had the lowest recorded HR of 50 to 59 bpm [8].The overall incidence of AF in general population varies from 1 to 2%, whereas among oncological patients, it reaches between 5% and 16%, depending on the risk factors and cancer type [3,4].

The incidence of VAs is smaller than in the case of atrial arrhythmias. However, the severity of the complications after the possible cardiac arrest is more serious. Several groups of medicines are known for prolonging QT, including antiarrhythmics, antidepressants, antifungals, or antiemetics. Other risk factors increasing the risk of VAs in cancer patients are electrolyte abnormalities and inadequately adjusted doses of renal or hepatic-cleared QT-prolonging drugs [3].

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Bradycardia is defined as a heart rate below 60 beats per minute. It is rather rare in oncological patients. The majority of bradyarrhythmia episodes are asymptomatic. Fortunately, there is rarely a need for adjusting the drug dose or other interventions.The best-known group of chemotherapeutics that is likely to cause bradycardia are anaplastic lymphoma kinase (ALK) inhibitors, for instance, crizotinib or ceritinib. They are used mainly in non-small cell lung cancer (NSCLC) treatment [4]. A retrospective analysis of 153 patients was conducted, including patients who had at least one pretreatment heart rate (HR) measurement and afterwards were given crizotinib in advanced NSCLC therapy. A total of 41.9% patients experienced at least one recorded episode of sinus bradycardia (SB). The mean maximum decrease of HR was 30.0 bpm. It was higher than in patients who did not experience sinus bradycardia, where the mean maximum decrease of HR was 21.4 bpm; 5.9% of 44 patients experienced the lowest HR below 45 bpm. The majority of patients (75.3%) had the lowest recorded HR of 50 to 59 bpm [8].

Arrhythmias occur more frequently in oncology patients. All cancers increase arrhythmia risk, but it can be lowered by adjusting drug dose or therapy type.

Risk Factors of Arrhythmias in Oncological Patients. Several risk factors increase the chance of arrhythmia in oncology patients. Some of these risk factors may overlap with those for cardiovascular disease, such as advanced age, race, endocrine and metabolic disorders. Additionally, many groups of medicines used in cancer treatment are known for their pro-arrhythmogenic effect. The risk factors can be categorized into four groups: non-chemotherapeutic factors (prior arrhythmogenic substrate, post-surgery arrhythmia, arrhythmogenic medications including antiemetics); cardiotoxicity of chemotherapeutic treatment; direct cardiac involvement (primary heart cancer, metastasis to the heart); and electrolyte abnormalities (resulting from vomiting or drug-induced) [5].

Management of Arrhythmias in Oncological Patients Atrial Fibrillation and Supra‑ventricular Tachycardia. The new guidelines on cardio-oncology suggest that the management of patients with cancer and concomitant AF should follow current ESC Guidelines for diagnosis and management of AF, with the use of the integrated ABC pathway (anticoagulation/avoid stroke, better symptom con- trol, cardiovascular risk factors, and concomitant diseases management). They also propose a new T-B-I-P algorithm (thromboembolic risk, bleeding risk, drug–drug interactions, patient preferences) to assess the risk of anticoagulation in patients with cancer and concomitant AF. The risk of stroke and systemic embolism should be evaluated with the CHA2DS2-VASc score, although it is not fully validated for use in oncological patients. Long-term anticoagulation must be considered in men with ≥1 point and women with≥ 2 points and is recommended in men with ≥ 2 points and

women with ≥3 points [6]. In patients with severe mitral stenosis or mechanical prosthetic valve vitamin K antagonists (VKA) are the drugs of choice. Low molecular weight heparin (LMWH) can be considered a short-term option in patients freshly diagnosed with cancer, with advanced cancer, or during anticancer treatment. New oral anticoagulants (NOAC) use in oncological patients is very limited, due to multiple drug-drug interactions, although recently made meta-analysis suggests their similar effectiveness compared to VKA treatment in patients with cancer [9]. The data on the usage of the left atrial appendage occluder devices have very limited data among this group of patients. The use of those devices can be associated with an increased risk of complications, such as device-related thrombosis in oncological patients [7].

The bleeding risk should be evaluated with a HAS-BLED score. The modifiable bleeding-promoting risk factors (for instance thrombocytopenia, recent major bleeding, gastro-intestinal cancer diagnosis) should be identified. The next step is assessing drug interactions taking into account anti-cancer agents as well as other supportive therapies. Finally, patients' preferences and drug availability should also be taken into account.

Ventricular Arrhythmias. Patients to be treated with drugs that have a high risk of QTc prolongation should have baseline 12-lead ECG performed and also modifiable risk factors of VA should be corrected. If the baseline QTc interval is ≤ 480ms, the therapy can be started under ECG monitoring. The ECG should be performed once the blood level of the anticancer drug is achieved, after every modification in the treatment, and once a month for the first 3 months. According to current ESC guidelines on cardio-oncology, QTc interval changes above 60ms, with QTc still < 500ms, should not affect oncological treatment.

Patients with QTc > 480ms require closer monitoring. Reversible causes of long QT interval should be corrected, ECGs performed weekly, the risk of VA evaluated during the treatment, and an alternative treatment considered. In patients with abnormalities in baseline QTc interval, patients with symptoms of arrhythmia or treated with QTc prolong- ing drugs cardiology consultation are advised.

The treatment of anticancer therapy-induced VA should follow general guidelines for the management of VA [10]. Asymptomatic episodes of VA that are self-terminating should not be a reason to terminate the oncological treatment, unless patients have persisting ECG abnormalities. The intervention is required in case of recurrent VA. However, the usage of anti-arrhythmic drugs is limited, due to drug-drug interactions and possible further QTc prolongation. Current ESC guidelines recommend beta-blockers and class IB antiarrhythmics as the safest option in the VA treatment, because they are less likely to interact with other drugs. Beta-blockers are

the drugs of choice when cancer drug is known to cause cancer therapy-related cardiac dysfunction. Amiodarone is preferred in patients, who have a structural cardiac disease or that are hemodynamically unstable. Decisions on the type of therapy should be made on an individual basis and should take into account factors, like complication risk or predicted life expectancy.

Bradycardia episodes secondary to cancer treatment are usually asymptomatic depending on the heart rate at the time of the episode [9]. Possible symptoms include dizziness, fatigue, pre-syncope, or syncope. If the patient is symptomatic, Holter-ECG is recommended to assess the severity of the bradycardia and exclude long sinus pauses. A trial of withdrawing anticancer drugs should be performed to confirm the coincidence with the symptoms. A multidisciplinary team should discuss the risks and benefits of continuing the treatment at a lower dose and eventually consider alternative therapy. The pacemaker implantation is indicated, when there is no substitution for the current treatment. The final decision should take into account patients' preferences and should be made after cardiologist and oncologist consultation.

Conclusions. Arrhythmias are more common in cancer patients than in the general population, regardless of the type of cancer. The incidence of arrhythmias depends on various factors such as the patient's characteristics, risk factors, cancer grade, and stage. Many cancer treatments, including anthracyclines, antimetabolites, TKIs, and immunotherapy, are known to be major risk factors for causing arrhythmias. It is important to follow specific guidelines for diagnosing and managing arrhythmias in cancer patients, considering both traditional factors and cancer-related issues such as cardiotoxicity of chemotherapy, direct cardiac involvement, and electrolyte imbalances.

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