Real world experience of the first cardio-oncology unit implantation in Morocco

ABSTRACT

Cardiotoxicity represents a complex challenge with far-reaching implications. This investigation into cardiotoxicity associated with anthracyclines and Trastuzumab has elucidated these agents as common culprits, unveiling a spectrum of cardiotoxicities beyond heart failure and arrhythmias to include hypertension, QTc prolongation, and arterial and venous thromboses. Nevertheless, the true prevalence of cardiotoxicity remains underestimated, owing to delayed effects, patient loss to follow-up post-remission, and the introduction of novel therapeutic molecules.

As we explore new frontiers, the collaboration between cardiology and oncology is broadening, incorporating Cardio-Hematology and its impact on conditions like multiple myeloma, leukemia, and lymphomas. This evolving intersection emphasizes the need for interdisciplinary cooperation.

The study findings underscore the importance of guideline adherence while recognizing that guidelines should serve as help rather than substitutes for clinical judgment in multidisciplinary tumor boards (MTBs). Enriched by ongoing research, these guidelines are tools empowering clinicians to make informed decisions tailored to individual patient profiles.

Scientific research remains pivotal, guiding progress and offering hope for improved outcomes in the global fight against cancer.

Keywords: Cardiotoxicity, Chemotherapy, Heart Failure, Cardio-oncology, Morocco

1. INTRODUCTION

Cardiovascular disease and cancer have many similarities, they are both leading causes of mortality worldwide [1, 2].

In response to the demand for guidance, The American Society of Clinical Oncology in 2017 [8] and more recently in 2022 the task force on cardio-oncology of the European Society of Cardiology in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) European society , published a comprehensive , exhaustive guidelines for the cardiovascular treatment of cancer patients. These guidelines advise doctors to do thorough cardiovascular evaluations on adult cancer patients, including screening for modifiable risk factors of CVD, as a baseline risk assessment, before start of any potentially cardiotoxic therapy. [8, 9]

We evaluated real life incidence of cardiotoxicity related to different chemotherapy regimen through follow up in an organized cardio-oncology unit, of different cohorts of cancerous patients stratified based on the regimen of treatment.

We also evaluated the pre therapeutic risk stratification and the mortality prevalence.

2. MATERIAL AND METHODS

Since 2017, a single-center registry has been developed jointly between the cardiology department and the oncology department of a tertiary university hospital in Casablanca, Morocco. In this context, a cardio-oncology unit, made up of cardiologist and oncologist, has been recruiting patients since that date.

A daily consultation is carried out in both the oncology and cardiovascular units. In cardiology, a follow-up protocol was established based on the ESC guidelines, including clinical, electrocardiographic (ECG), echocardiography and laboratory assessment, including cardiac biomarkers.

Toxicity management is carried out jointly once a month, where shared decisions are made within a multidisciplinary team following international guidelines and where personalized monitoring is decided.

Study population

Duration: Between January 2017 and November 2022

Study Population: Patients diagnosed with cancer, whose treatment would include a chemotherapy with cardiotoxic medication, or had a known cardiovascular disease

Inclusion criteria:

Patients histologically diagnosed with a cancer, candidate for a chemotherapy that includes a cardiotoxic medication and/or had a known cardiovascular disease and admitted to the cardio-oncology unit before receiving their first chemotherapy.

Exclusion criteria:

- Missing data concerning cardiovascular evaluation before receiving chemotherapy
- Patients who had already started chemotherapy regimen before their first cardiovascular evaluation

Recruitment centers are Ibn Rochd University Hospital and Mohammed VI Cancer Center.

A total of 2883 patients with a histological diagnosis of cancer were sequentially recruited. Patients (n= 516) who had already begun chemotherapy, or lacking data were excluded.

After exclusion of this subgroups, we analyzed data of 2367 patients

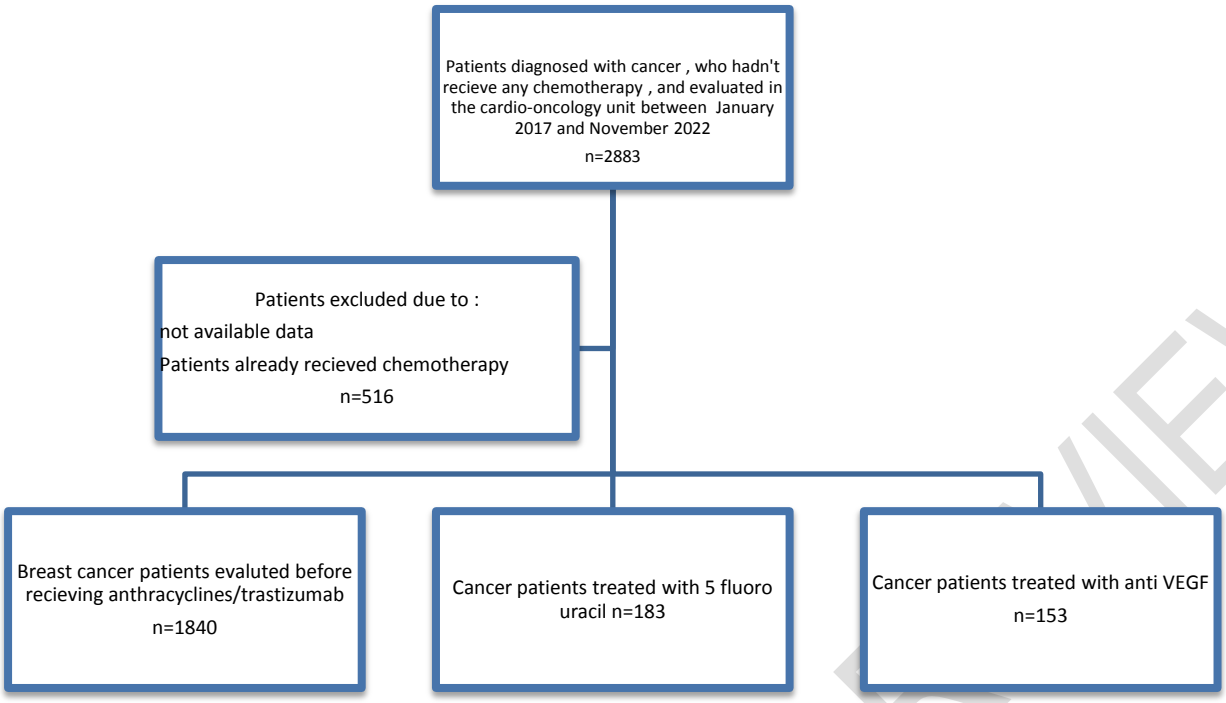

Fig 1. Flow chart showing study protocol

In response to the demand for guidance, The American Society of Clinical Oncology in 2017 [8] and more recently in 2022 the task force on cardio-oncology of the European Society of Cardiology in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) European society , published a comprehensive , exhaustive guidelines for the cardiovascular treatment of cancer patients. These guidelines advises doctors to do thorough cardiovascular evaluations on adult cancer patients, including screening for modifiable risk factors of CVD , as a baseline risk assessment, before start of any potentially cardiotoxic therapy . [8,9]

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We also evaluated the pre therapeutic risk stratification and the mortality prevalence.

Ethical approval

The appropriate institutional committees granted their approval in terms of ethics. All participants gave their consent in writing after being fully informed. The study was conducted in accordance with the Helsinki Declaration's ethical guidelines.

Data collection and study variable

During patient visits to the hospital, participants were recruited. Face-to-face history taking was used to collect information on age the diagnosis, medical history (including previous diagnoses of hypertension, diabetes mellitus, dyslipidemia, and CVD as myocardial infarction, chronic coronary syndrome, heart failure and stroke), other comorbidities and medications use. Additionally, information on smoking habits and history of hereditary coronary heart disease was collected.

Examinations included measurements of body weight, height, and body mass index (BMI). If the calculated BMI was 30 kg/m2 or more, obesity was noted. Using automated sphygmomanometers, systolic and diastolic chamber blood pressure values were taken. There were signs of hypertension

Patients were considered to have hypertension if they reported having it or were taking medications to treat it and/or had persistently high blood pressure (systolic > 140 mmHg or diastolic > 90 mmHg) (measured at least twice).

To test blood lipid and glucose levels, non-fasting blood samples were taken. Patients were considered to have dyslipidemia if they reported having it, were taking medications to lower their cholesterol levels, had a serum total cholesterol level greater than 2 g/L, or had a serum low-density lipoprotein level (LDL) greater than 1.6 g/L. [14]. Based on patient self-report, medication use, and/or fasting blood glucose greater than 1.26 mg/L, diabetic status was documented.

Data on tumor characteristics were obtained from oncology records (date of diagnosis, histology, tumor size at presentation, distant metastases at initial diagnosis (yes or no), TNM stage (I, II, III, IV), progesterone and estrogen receptor status (positive or negative).

Monitoring of cardiac function during treatment and prediction of cardiotoxicity

The Cardiotoxicity Risk Score, a risk-stratification tool created by the Mayo Clinic [11] that enables doctors to classify cancer patients into very low, low, intermediate, high, and very high cardiotoxicity risk groups based on a set of patients- and cancer treatment-related risk factors, was then used to determine individual risk of cardiotoxicity. One point was deducted from a candidate's score if they had a history of hypertension, diabetes, cardiomyopathy, or heart failure, being female, younger than 15 or older than 65, having a history of coronary artery disease, having received prior or ongoing anthracycline-based chemotherapy, or having received prior or ongoing chest radiation. Patients who took cardiotoxic medications like cyclophosphamide, anthracycline, or trastuzumab could score up to four points. A total score of under two was thought to suggest a low risk of cardiotoxicity, whereas scores between three and four indicated an intermediate risk, scores between five and six indicated a high risk, and scores over six indicated a very high risk [11].

We used to stratify patients in one of the four categories mentioned above the proposed ESC calculator of risk score specific to the molecule used in treatment . [9]

3. RESULTS AND DISCUSSION

Statistical data analysis was performed using Microsoft Excel 2022. The statistical significance was set at a p value <0.05. Data analysis started with standard descriptive methods to describe the data (means and standard deviations) and then multivariate analysis was used to test statistical significance.
In this group of patients with newly discovered cancer, the baseline prevalence of conventional cardiovascular risk factors is like following:

- Previously diagnosed hypertension prevalence was 18.74%
- 13.1% of patients had diabetes mellitus at the time of their initial cancer diagnosis
- At the outset, the prevalence of obesity was 8.6 %
- Roughly 6.6%of patients had dyslipidemia at presentation.
- A percentage of 8% reported smoking.
- Menopaused women represented 56% of all female patients included.

The gathering of CVD risk factors was significant in cancer patient population, where 57.9% of patients had at least one modifiable risk factors at baseline and more specifically 37.4%, 13.4% and 5.4 % had respectively one, two and three risk factors when their cancer was first diagnosed. (Figure 2)

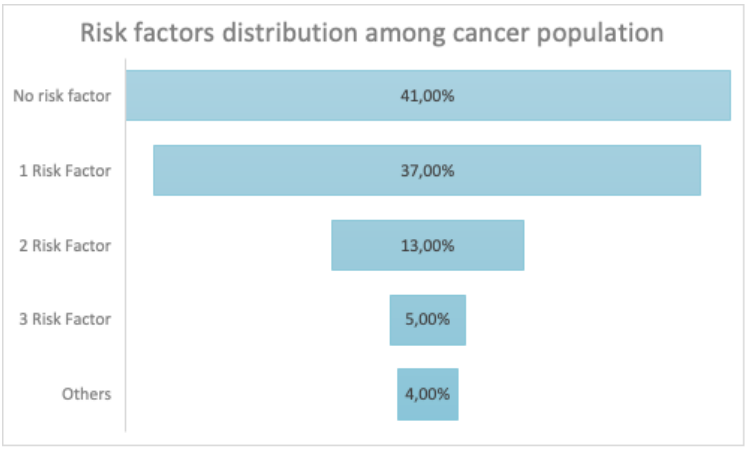

Figure 2. Risk factors distribution among cancer population

Four percent of the patient cohort exhibited cardiovascular disorders. Within this subset, the predominant condition was heart failure, accounting for 64% of cases, with 47% of these individuals having documented ischemic heart disease confirmed through coronary angiography (including a history of myocardial infarction, coronary heart disease, chronic coronary syndromes, or prior coronary percutaneous intervention). Additionally, valvular disease manifested in 35% of the cases within this cardiovascular subgroup.
Patients were categorized into risk groups (Very High Risk, High Risk, Moderate Risk, and Low Risk) using the HFA-ICOS Baseline Risk Assessment with simplified bedside application of the Pocket ESC.

The results of risk stratification (Figure 3) were as follows:

- Low Risk: 42%
- Moderate Risk: 46%
- High Risk: 9%
- Very High Risk: 3%

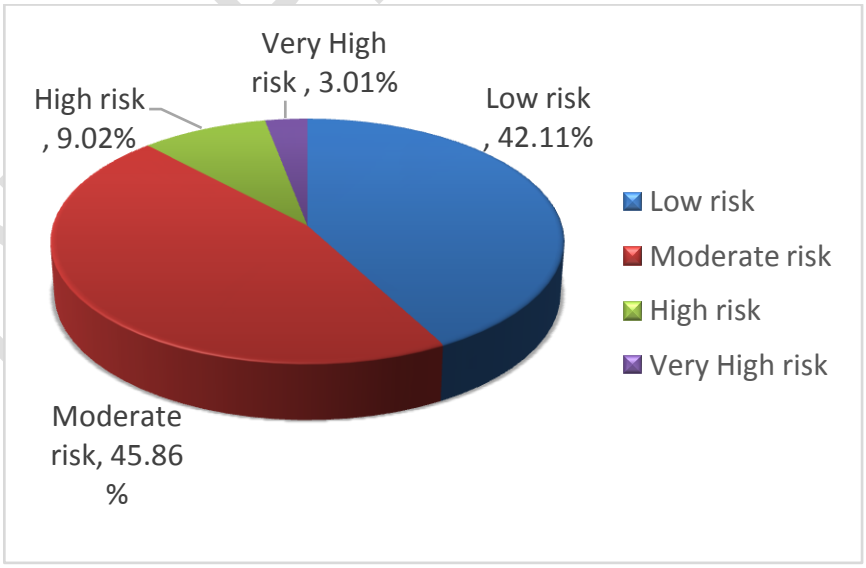

Figure 3: Risk Stratification prior to chemotherapy using HFA-ICOS Baseline Risk

Sub-groups results analysis based on the molecule of treatment was as the following :

1/Anthracyclines/Trastizumab :

In the investigation of the subgroup receiving anthracycline chemotherapy, the key findings are summarized below:

Prevalence of Anthracycline Utilization:

Anthracycline chemotherapy was administered to approximately 80% of the patients in our study, reflecting the widespread use of these agents in clinical oncology, as breast cancer represented the predominant cancer , and anthracyclines is the gold standard treatment.

Dosing Regimens:

Doxorubicin was administered at an average dose of 60 mg/m² every 21 days.

Epirubicin was given at an average dose of 100 mg/m² every 21 days.

Among the patients in the study, 9% received a cumulative dose exceeding 500 mg/m² of anthracyclines, and 47% received cumulative doses ranging from 250 to 500 mg/m², underscoring the common usage of these agents and the potential implications for cardiotoxicity related to the dosage.

Cardiotoxicity Incidence:

Among the patients studied, a total of 135 cases of cardiotoxicity related to anthracycline and/ or Anti HER2 treatment were identified

In this study the reversibility of cardiotoxicity was observed in 45 female patients who were HER2 positive for the receptor, suggesting that in a subset of individuals, cardiotoxic effects associated with anti HER2 therapy chemotherapy may be ameliorated or reversed with appropriate interventions, including prompt interruption and cardioprotective measures.

Utilization of Anti-HER2 Therapies:

Among the patient cohort, 1117 patients were concurrently receiving anti-HER2 therapies in conjunction with anthracycline-based chemotherapy regimens.

These findings emphasize the complexity of anthracycline chemotherapy and its potential impact on cardiotoxicity. The data presented here underscore the need for individualized treatment strategies, vigilant monitoring, and consideration of concurrent therapies, particularly in patients receiving anti-HER2 agents alongside anthracyclines.

2/ 5-FU Regimens:

In the subgroup of patients who received 5-fluorouracil (5-FU) in various treatment regimens (including Folfox and Capecitabine), we observed 14 cases of cardiotoxicity.

The distribution of neoplasms was as follows: 61% rectum, 22% colonic, and 17% gastric

The breakdown of cardiotoxicity manifestations within this subgroup was as follows: 14% experienced coronary spasms, 7% had myocardial infarctions (IDM), 22% exhibited alterations in global longitudinal strain, and 57% reported chest pain.

These findings illuminate the multifaceted landscape of cardiotoxicity in cancer patients receiving 5-FU-based chemotherapy regimens as opposed to anthracyclines.

3/Anti-VEGF Therapy (Bevacizumab):

In our cohort, 152 patients were receiving Anti-VEGF therapy with Bevacizumab, a targeted therapy.

The distribution of cancer types among the patients was as follows: 41% ovarian, 24% rectal, and 31% colonic.

Among those receiving Bevacizumab, 38 cases of cardiotoxicity were identified.

Types of cardiotoxicities observed in the study included:

- 11 cases of hypertension (HTA) grade 2 and 3
- 4 ischemic events, including renal infarcts and coronary artery occlusions.
- 5 thrombotic events, including deep vein thrombosis.

4/ Patients Evolution:

We tracked the progression and outcomes of the study participants. Understanding the evolution of patients is crucial in assessing the long-term effects of treatment. The patient follow-up data is summarized below:

Patients Currently Under Follow-Up: Out of the cardiotoxic study cohort, 76 patients are currently under active follow-up. These patients are regularly monitored to assess their ongoing health status, including cardiac function and overall well-being .

Patients Lost to Follow-Up: 43 patients from the original cohort were lost to follow-up. This can occur for various reasons, including changes of contact information, transfer to other healthcare facilities, or patient choices. Efforts to reestablish contact with these patients are ongoing to ensure their outcomes are accurately assessed.

Deceased Patients: Regrettably, 14 patients from the study cohort have passed away during the course of the study.

Discussion:

The study of this cohort showed that patients with cancer presented with a high baseline of modifiable risk factors for CVD.

Those patients showed a baseline prevalence of hypertension, diabetes, and dyslipidemia that is similar to what was reported in the literature. [10, 11]. In the LACE Study [12], hypertension was independently linked to an elevated risk of all-cause death and also among early-stage breast cancer survivors. Another prior study had revealed that breast cancer patients with diabetes were more likely than those without diabetes to require hospitalization for toxicity brought on by chemotherapy.[13]

The existence of any additional CVD risk factors at baseline was linked to an increased incidence of cardiac events and death, according to clinical trials data of breast cancer population.[14].

In the present study, we demonstrated that the association of pre-existing cardiac disorder, such as ischemic heart disease or cerebrovascular disease, appears to be consistently associated with reduced use of adjuvant therapies. Our observations are consistent with data from a previous population-based study , in which women with breast cancer who had a history cardiovascular disease or stroke were less probable to get the recommended treatment of cancer, including chemotherapy (OR: 0.56; 95% CI:0.48–0.66) and radiotherapy (OR:0.75; 95% confidence interval:0.67-0.83) [15].

Our research supports the idea that cardiovascular risk factors as hypertension, diabetes, obesity should be taken into account when deciding how to treat cancer.

Many risk score has been developed in order to stratify patients receiving chemotherapy to different categories based on the risk of cardiotoxicity's occurrence , the most recent one is HFA-ICOS proposed by the Heart Failure Association (HFA) Cardio-Oncology working group and the International Cardio Oncology Society (ICOS) , and recently validated in clinical studies including patients receiving anthracyclines [16] and also patients with chronic myeloid leukemia [17]. The results of this validity testing demonstrated a good performance to predict all-cause mortality and cardiotoxicity occurrence.

The latest ESC guidelines published in 2022, introduced the toolkit for risk stratification by using the Pocket guidelines algorithm to categorize the patients to one of the four subgroups: Low risk, Moderate Risk, High Risk , Very High risk [9].

This model could allow optimization of cancer treatment, with early referral to a cardiologist, cardiovascular monitoring, and early screening of at-risk individuals who may benefit from cardioprotective therapy prescription [7].

Our findings highlight the need to incorporate and support rigorous cardiac follow-up, closly heart monitoring, and coordinated multidisciplinary care especially in High and Very High risk subgroups. That's why, cardiotoxicity prediction scores provide a way to combine information on patient-related cardiovascular risk factors with information on cancer treatment-related factors, resulting in the estimation of cardiotoxicity prediction probability to help with risk stratification for people recently diagnosed with cancer.

The Cardiotoxicity of Anthracyclines:

Anthracyclines, a cornerstone in cancer chemotherapy, have long been known for their significant therapeutic efficacy; however, they also carry a well-documented risk of cardiotoxicity, a concern highlighted by our study results which include 1840 patients. The prevalence and incidence of anthracycline-induced cardiotoxicity have been extensively studied in the literature, with reported rates varying from 5% to 30%, contingent upon factors such as cumulative dose, age, and concomitant therapies [18]. Our findings highlight this variability, as our incidence percentage is 1% which may be due to the large volume of our cohort, close monitoring and early start of cardioprotective measures, underlining the importance of individualized risk assessment and vigilant cardiac monitoring. Cardiotoxicity, if left unchecked, can lead to adverse outcomes, including heart failure and compromised quality of life [19].

The mechanisms of anthracycline-induced cardiotoxicity are complex and multifactorial. These agents are known to generate reactive oxygen species (ROS), leading to oxidative stress within cardiac myocytes [20]. This oxidative stress can result in damage to cellular components, including lipids, proteins, and DNA, ultimately contributing to cardiomyocyte injury and apoptosis [21]. Anthracyclines may also disrupt mitochondrial function, impair calcium homeostasis, and induce inflammation in the myocardium, collectively leading to cardiac dysfunction [22].

In the context of targeted therapies, the introduction of Trastuzumab (Herceptin) for HER2-positive breast cancer patients has significantly improved outcomes. However, this therapeutic advancement has also introduced additional considerations regarding cardiotoxicity. Trastuzumab-associated cardiotoxicity, while generally reversible, poses a unique challenge when administered sequentially with anthracyclines, as evidenced by this study [23]. The latest guidelines, such as those developed by the European Society of Cardiology (ESC), emphasize the critical importance of risk stratification before initiating cancer treatment . Risk stratification enables healthcare providers to identify patients at higher risk of cardiotoxicity and tailor their treatment regimens accordingly. Dexrazoxane, an iron-chelating agent, has shown promise in reducing cardiotoxicity when administered concurrently with anthracyclines [24]. Furthermore, the implementation of cardioprotective agents and early intervention holds potential for improving long-term patient outcomes [25].

A multidisciplinary approach to cancer care is crucial, with cardiologists and oncologists collaborating to ensure optimal risk stratification, treatment, and follow-up care. This study underscores the necessity of collaboration between cardiologist and oncologist for the monitorringand long-term follow-up for cancer survivors. This is evident from previous research that some cardiotoxic effects may be reversible, particularly with trastusumab and with appropriate interventions [26].

Multidisciplinary team meetings to refine our understanding of cardiotoxicity linked to anthracyclines and trastuzumab, personalized risk assessment and tailored management strategies, guided by the latest guidelines, will play a pivotal role in optimizing the balance between the curative potential of these agents and their potential for heart damage.

5 FU cardiotoxicity:

5-fluorouracil (5-FU) has played a vital role in cancer management digestive ones. it is often employed in regimens such as Folfox and Capecitabine. However, it is crucial to acknowledge the potential cardiotoxicity associated with this agent. The incidence of cardiotoxicity with 5-FU varies across studies, with manifestations ranging from coronary spasms to myocardial infarctions and alterations in global longitudinal strain [27]. While the exact cause of 5-FU-induced cardiotoxicity is not fully elucidated, several mechanisms have been suggested:

Coronary Vasospasm: Where 5-FU can lead to the constriction of coronary arteries. Which reduces blood flow to the heart muscle, leading to angina-like chest pain or even myocardial infarction (heart attack). The spasm of coronary vessels may be triggered by the direct toxic effects of 5-FU on vascular smooth muscle cells [28]

Endothelial Dysfunction: 5-FU may impair the function of endothelial cells. Endothelial dysfunction can disrupt the balance of vasodilators and vasoconstrictors, further contributing to coronary vasospasm and reduced blood flow. Thrombosis: There is evidence to suggest that 5-FU may increase the risk of blood clot formation (thrombosis) within the coronary arteries. This can lead to partial or complete blockage of blood flow, resulting in ischemic events, such as myocardial infarction.[29]

The inflammatory Response: Some studies propose that 5-FU treatment may trigger an inflammatory response in the vascular system, leading to endothelial damage and increased susceptibility to coronary artery spasm.[28]

Individual Susceptibility: Genetic factors and individual patient characteristics may also play a role in determining susceptibility to 5-FU-induced cardiotoxicity. Some patients may have genetic variations that make them more prone to adverse cardiovascular effects.

Our study, consistent with existing literature, observed cardiotoxic effects in a subset of patients receiving 5-FU-based therapies, underlining the need for comprehensive cardiac monitoring.

Comparatively, the cardiotoxicity profile associated with 5-FU differs from that of anthracyclines and anti-VEGF therapies, highlighting the heterogeneous nature of cardiotoxic effects induced by diverse cancer treatments. However, like other treatments, personalized risk assessment remains vital [30]. The management strategies discussed in our study, including early detection and intervention, align with principles established for other cardiotoxic agents [25].

Our findings underscore the importance of long-term follow-up for cancer survivors exposed to 5-FU, as some cardiotoxic effects may be reversible with timely interventions . Collaborative care involving oncologists and cardiologists is instrumental in optimizing treatment outcomes while managing potential cardiac risks.

As we continue to explore the complexities of 5-FU-related cardiotoxicity, personalized risk assessment and tailored management strategies, informed by the latest guidelines, will be central in achieving the delicate balance between the therapeutic benefits of 5-FU and its potential for cardiac injury.

Anti VEGF therapy :

Cardiotoxicity associated with anti-VEGF (Vascular Endothelial Growth Factor) therapy, exemplified by Bevacizumab, represents a multifaceted challenge in the landscape of cancer treatment.

Bevacizumab, a monoclonal antibody targeting VEGF, has emerged as a valuable tool in the inhibition of tumor angiogenesis, demonstrating substantial efficacy in various malignancies. However, this therapeutic advancement has brought to light the potential for cardiovascular adverse effects. The prevalence and incidence of cardiotoxicity with anti-VEGF agents can vary, influenced by factors such as the specific agent, dose, treatment duration, and underlying patient cardiovascular risk factors [31]. Our study, aligning with existing literature, identified 25% cases of cardiotoxicity associated with Bevacizumab among our cohort of 152 patients receiving this treatment , dominated by hypertension . [32]

Bevacizumab-induced cardiotoxicity presents a diverse spectrum of manifestations, encompassing conditions such as hypertension, heart failure, myocardial ischemia, and thromboembolic events [33]. The mechanisms underlying this cardiotoxicity are complex and multifactorial. While the inhibition of VEGF can lead to hypertension through impaired nitric oxide-mediated vasodilation, other contributing factors may include endothelial dysfunction, impaired cardiac function, and increased risk of thrombosis [34]. Additionally, individual patient characteristics and pre-existing cardiovascular risk factors play a pivotal role in determining susceptibility to Bevacizumab-related cardiotoxicity [35].

Management of Bevacizumab-induced cardiotoxicity necessitates a systematic approach. Early detection by systematic arterial pressure monitoring through during treatment is vital, allowing for timely intervention and dose modifications when necessary . Collaborative care in a cardio-oncology unit is imperative, enabling risk stratification and tailored management.

The latest guidelines underscore the importance of comprehensive risk assessment before initiating anti-VEGF therapy to identify patients at higher risk of cardiotoxicity and tailor treatment plans accordingly [9]. As we continue to explore the intricate relationship between anti-VEGF therapies and cardiotoxicity, personalized risk assessment and evidence-based management strategies will be pivotal in optimizing cancer treatment while safeguarding patients' cardiac function.

However Some limitations need to mention. The design of our study was not population-based as in epidemiology research studies ; hence , the prevalence results should be interpreted with caution. As This study was performed with conjunction beteween in cardiologistes teams and oncologists, most patients reffered to assessement were selected based on medical history , symptoms or the treatement regimen planned to be prescribed . Therefore, proporitionsof cancer types had uneven distribution, as welle as the gender prevalence as females were more represented due to the high proportion of patients with breast cancer receiving anthracyclines . Our study doesn't represent an external validation on population of any current risk prediction score , but solely an epidemiological descriptive observation of a local population .

4. CONCLUSION

Cardiotoxicity is a multi-faceted challenge. Our exploration of cardiotoxicity associated with anthracyclines and Trastuzumab has revealed that while these agents are indeed the most common culprits,

This study has shed light on the diverse types of cardiotoxicities, ranging from heart failure and arrhythmias to hypertension, QTc prolongation, arterial and venous thromboses. However, it is crucial to recognize that the true prevalence of cardiotoxicity remains underestimated. This underestimation can be attributed to delayed effects, patients lost to follow-up after remission, and the introduction of new therapeutic molecules that introduce novel dimensions to this complex issue.

As we delve into new horizons, we are witnessing the emergence of new facets of cardiotoxicity in collaboration with fields like Cardio-Hematology, encompassing conditions such as multiple myeloma, leukemia, and lymphomas. These expanding dimensions remind us that the intersection of cardiology and oncology continues to evolve, demanding interdisciplinary cooperation.

This study findings reinforce the importance of adhering to guidelines while acknowledging that they should serve as guides rather than replacements for clinical judgment in multidisciplinary tumor boards (MTB or RCP in frensh). These guidelines, enriched by ongoing research, should be viewed as tools that empower clinicians to make informed decisions tailored to individual patient profiles.

Scientific research remains the cornerstone of progress and the beacon guiding us toward improved outcomes for cancer patients worldwide.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this study. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

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