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RESEARCH

SIGNS AND SYMPTOMS OF CARDIOTOXICITY IN CANCER PATIENTS UNDERGOING ANTINEOPLASTIC THERAPY: SCOPING REVIEW*

*SINAIS E SINTOMAS DE CARDIOTOXICIDADE EM PACIENTES COM CÂNCER SUBMETIDOS À TERAPIA ANTINEOPLÁSICA: REVISÃO DE ESCOPO**

*SIGNOS Y SÍNTOMAS DE CARDIOTOXICIDAD EN PACIENTES CON CÁNCER: REVISIÓN DE ALCANCE**

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ABSTRACT

Objective: to map the signs and symptoms of adult patients undergoing cardiotoxic antineoplastic therapy. **Method**: scope review according to Joana Briggs Institute (JBI). The search was carried out in Medline/PubMed, LILACS/BVS, Cochrane Library/Wiley, CINAHL and SCOPUS in December 2021. The studies were managed by Endnote and selected in Rayyan, based on the selectivity criteria. **Results**: 297 studies were identified and of these 25 were included in the review. Signs and symptoms of direct and indirect cardiovascular damage associated with structural, functional and ischemic changes were mapped. **Conclusion**: the most cited signs and symptoms in the studies were chest pain, decreased ejection fraction, heart failure, arrhythmias and dyspnea. The mapping presented in this study can contribute to their early recognition and guide health practice.

Keywords: Antineoplastic Agents; Cardiotoxicity; Neoplasms; Medical Oncology; Signs and Symptoms.

RESUMO

Objetivo: *mapear os sinais e sintomas de pacientes adultos submetidos à terapia antineoplásica cardiotóxica.* ***Método***: *revisão de escopo de acordo com a metodologia do Instituto Joana Briggs. A busca foi realizada nas bases Medline/PubMed, LILACS/BVS, Cochrane Library/Wiley, CINAHL e SCOPUS em dezembro de 2021. Os estudos foram gerenciados pelo Endnote e selecionados no Rayyan, de acordo com os critérios de elegibilidade.* ***Resultados***: *foram identificados 297 estudos e destes, 25 foram incluídos na revisão. Foram mapeados sinais e sintomas de danos cardiovasculares diretos e indiretos, associados a alterações estruturais, funcionais e isquêmicas.* ***Conclusão***: *os sinais e sintomas mais frequentemente citados nos estudos foram dor torácica, diminuição da fração de ejeção, insuficiência cardíaca, arritmias e dispneia. O mapeamento apresentado neste estudo pode contribuir para o reconhecimento precoce desses sinais e sintomas, direcionando a prática em saúde.*

Palavras-chave: *Antineoplásicos; Cardiotoxicidade; Neoplasias; Oncologia; Sinais e Sintomas.*

RESUMEN

Objetivo: *Mapear los signos y síntomas de pacientes adultos en tratamiento con antineoplásicos cardiotóxicos.* ***Método:*** *Revisión de alcance según metodología Joana Briggs Institute. La búsqueda se realizó en Medline/PubMed, LILACS/BVS, Cochrane Library/Wiley, CINAHL y SCOPUS en diciembre de 2021. Los estudios fueron administrados por Endnote y seleccionados en Rayyan, con base en los criterios de selectividad.* ***Resultados:*** *se identificaron 297 estudios y de estos 25 se incluyeron en la revisión. Se mapearon signos y síntomas de daño cardiovascular directo e indirecto asociados a cambios estructurales, funcionales e isquémicas.* ***Conclusión:*** *Los signos y síntomas más citados en los estudios fueron dolor torácico, fracción de eyección disminuida, insuficiencia cardiaca, arritmias y disnea. El mapeo presentado en este estudio puede contribuir para su reconocimiento temprano y orientar la práctica en salud.*

Palabras clave: *Antineoplásicos; Cardiotoxicidad; Neoplasias; Oncología Médica; Signos y Síntomas.*

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INTRODUCTION

Oncology has gained significant prominence in recent years. Cancer has become the second biggest cause of mortality in the world population, behind only cardiovascular diseases[1-2]. In the last 20 years, due to technological modernization and the progress and advancement of antineoplastic therapy, the survival rate of cancer patients has increased significantly. However, to achieve this result, a considerable price was paid, due to the severity of the adverse effects of intensive cancer treatment. Innovative therapies, with acute and late effects, affected patients' quality of life[1-5].

During the first decade of the 21st century, many questions arose about the relationship between cardiovascular changes and cancer treatment. Chemotherapy aims to induce cellular apoptosis or rapid necrosis of cancer cells, often with action also aimed at reducing tumor growth and suppressing cancer angiogenesis. When these mechanisms affect the heart, they cause toxic effects known as cardiotoxicity[2-5].

In clinical practice, with improving patient survival rates, the cardiovascular effects of cancer therapy are becoming increasingly relevant. The need to balance the objectives of antineoplastic treatment with cardiological objectives is evident. Collaboration between cardiology and oncology plays a crucial role in reducing adverse cardiovascular effects and achieving better results in cardiotoxic antineoplastic therapies[2-5]. The tendency to use progressively higher doses of cardiotoxic antineoplastic drugs, such as anthracyclines, the introduction of new antitumor agents that are also harmful to cardiac cells, chemotherapy interactions and the combination of radiotherapy increase the harmful effects on cardiac cells. The emergence of this complication without adequate monitoring and management can lead to the interruption of chemotherapy, compromising the cure of cancer or its adequate control[2-5].

Given this, early recognition of the signs and symptoms of cardiotoxicity is essential to ensure quality care and clinical decision-making in cardio-oncological health practice. With the aim of identifying what has already been produced in the literature in a consistent manner and using appropriate methodology, this study proposes to map the signs and symptoms of adult patients undergoing cardiotoxic antineoplastic therapy based on the following question: What are the signs and symptoms of cardiotoxicity in adult cancer patients undergoing antineoplastic treatment?

METHOD

This is a scoping review, conducted according to the methodology of the Joana Briggs Institute, systematized by the PCC[6] strategy, which represents an acronym for P (Population) adult patient with cancer, C (Concept) signs and symptoms and C (Context) cardiotoxicity. The review was registered in The Open Science Framework under the identification DOI: 10.17605/OSF.IO/XRK8M, being developed and structured based on the recommendations of the international guide Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA–ScR)[7-8].

Eligibility Criteria

Inclusion criteria: studies that addressed the signs and symptoms of cardiotoxicity in adult cancer patients, over 18 years of age, with any type of cancer were considered. The following types of sources were included in this review: descriptive, qualitative, methodological, conceptual and/or reflection studies, randomized controlled clinical studies, with an experimental or quasi-experimental design; time series or control case. Reviews of any nature were considered to identify studies cited in references, and not for inclusion in the mapping. Gray literature was also considered, such as dissertations and theses. The search limits were defined as documents published in English, Spanish or Portuguese, with no time limit. Exclusion criteria: studies without methodological description and/or with an approach to the topic that does not correspond to the PCC.

Source of Information

The bibliographic search was carried out on December 28, 2021, in the following databases: Medline/PubMed of the National Library of Medicine, Latin American and Caribbean Literature in Sciences and Health (LILACS) of the Regional Portal of the Virtual Health Library (VHL), Cochrane Library (Wiley), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and SCOPUS (Elsevier) from the Capes Journal Portal. A search for gray literature was also carried out in Open Access Theses and Dissertations (OATD).

Search Strategy

The terms were identified in the Health Sciences Descriptors (DeCS), Medical Subject Heading (MeSH) and

CINAHL Headings and these were related to the Boolean operators AND for intersection of sets and OR for sum of terms. The search strategy considered the intersection of terms referring to Population, Concept and Context of the PCC.

Table 1- Database search strategy

DATABASE	SEARCH STRATEGY
MEDLINE/ PUBMED	("neoplasms"[mh] OR "neoplasms"[All]) AND ("Signs and Symptoms"[mh] OR ("signs"[All] AND "symptoms"[All) OR "signs and symptoms"[All]) AND ("cardiotoxicity"[mh] OR cardiotoxicity[all])
Cochrane Library	neoplasm OR neoplasms in Title Abstract Keyword AND "Signs and Symptoms" OR signs OR symptoms in Title Abstract Keyword AND cardiotoxicity in Title Abstract Keyword
LILACS	(neoplasm OR neoplasms OR neoplasia*) AND ("Signs and Symptoms" OR signs OR symptoms OR "sinais e sintomas" OR sinais OR sintoma*) AND (cardiotoxicity OR cardiotoxidade) AND (db:("LILACS" OR "IBECS" OR "CUMED" OR "BDENF" OR "BIGG" OR "BRISA"))
CINAHL	((TI neoplasm OR neoplasms) OR (SU neoplasm OR neoplasms) OR (AB neoplasm OR neoplasms)) AND ((TI "Signs and Symptoms" OR signs OR symptoms) OR (SU "Signs and Symptoms" OR signs OR symptoms) OR (AB "Signs and Symptoms" OR signs OR symptoms)) AND ((TI cardiotoxicity) OR (SU cardiotoxicity) OR (AB cardiotoxicity))
SCOPUS	(TITLE-ABS-KEY(neoplasm OR neoplasms) AND TITLE-ABS-KEY("Signs and Symptoms" OR signs OR symptoms) AND TITLE-ABS-KEY(cardiotoxicity))
OATD	neoplasm* AND cardiotoxicity

Source: The authors, Niterói, Rio de Janeiro, Brazil, 2023

Selection of evidence sources

The search results were imported into the Endnote reference manager to identify duplications; afterwards, they were exported to the Qatar Computing Research Institute (QCRI) Rayyan application, where the selection process was carried out by title and abstract analysis, enabling blind selection and individual and simultaneous selection. The selection by title and abstract was carried out by two independent reviewers, and the studies included for evaluation of the full text were controlled in an Excel spreadsheet generated from Rayyan. Divergences regarding the inclusion or exclusion of articles were resolved after discussion and consensus among the researchers. Studies that met the inclusion criteria were read in full and evaluated in detail during data extraction.

Data Extractions

The data extraction and grouping process was carried out by two reviewers, independently, filling out a pre-prepared spreadsheet in the Microsoft Excel text editor. The divergences found were treated individually to unify the data and reach consensus among the reviewers. The variables used in data extraction were predefined and simplified. In Table 2, for the description of the authors, the names mentioned on the first page of each study were considered, the country where the study was published, the study design, the methodology used, and the population (sample, gender, age range and type of cancer), the antineoplastic drug involved and the concept, signs and symptoms of cardiotoxicity. In Table 2 - number of studies, signs and symptoms of cardiotoxicity, type of cancers and antineoplastic drugs involved.

Summary of Results

The included studies were synthesized and analyzed narratively, graphically and through tables. Results tables, the PRISMA-ScR flowchart and a word cloud, built in Pro Word Cloud, a Windows extension, are presented, which enabled the hierarchical presentation of the most cited signs and symptoms of cardiotoxicity in the included articles.

Ethical Aspects

As this is a secondary study that exclusively uses scientific texts, this scoping review does not require consideration by the Research Ethics Committee.

RESULTS

The search strategy allowed us to identify 297 articles, of which 22 were excluded due to duplication and 275 articles were entered into Rayyan to be analyzed by two independent reviewers based on reading the titles and abstracts, considering the inclusion and exclusion criteria. This led to the exclusion of 209 articles that did not meet the criteria. Therefore, a total of 66 articles were selected for full reading, of which 41 were excluded for not addressing the study question (PCC). Finally, 25 eligible studies were included and allowed qualitative analysis[9-33]. The PRISMA-ScR flowchart (Figure 1) demonstrates all bibliographic searches and the selection process, from identification to the final inclusion of studies, as shown in Figure 1.

Characteristics of evidence sources

To ensure comprehensive coverage, the data extracted from the 25 included articles were described in detail in Table 2. The included studies were analyzed qualitatively and, in terms of methodology, 12 (48%) were case studies, 12 (48%) were observational and 1 (4%) was a clinical trial. The articles were published in 16 different nationalities, with 6 (24%) studies conducted in the USA, 3 (12%) in Sweden, 2 (8%) in Italy and 2 (8%) in Japan. The remaining countries had only one publication. All studies were published between 1982 and 2017, with 6 (24%) published in 2017. The summary of the characteristics of the studies, including authorship, year of publication, country, study design, population, antineoplastic drugs and signs and symptoms of cardiotoxicity, is presented in Table 2 in descending chronological order of publication.

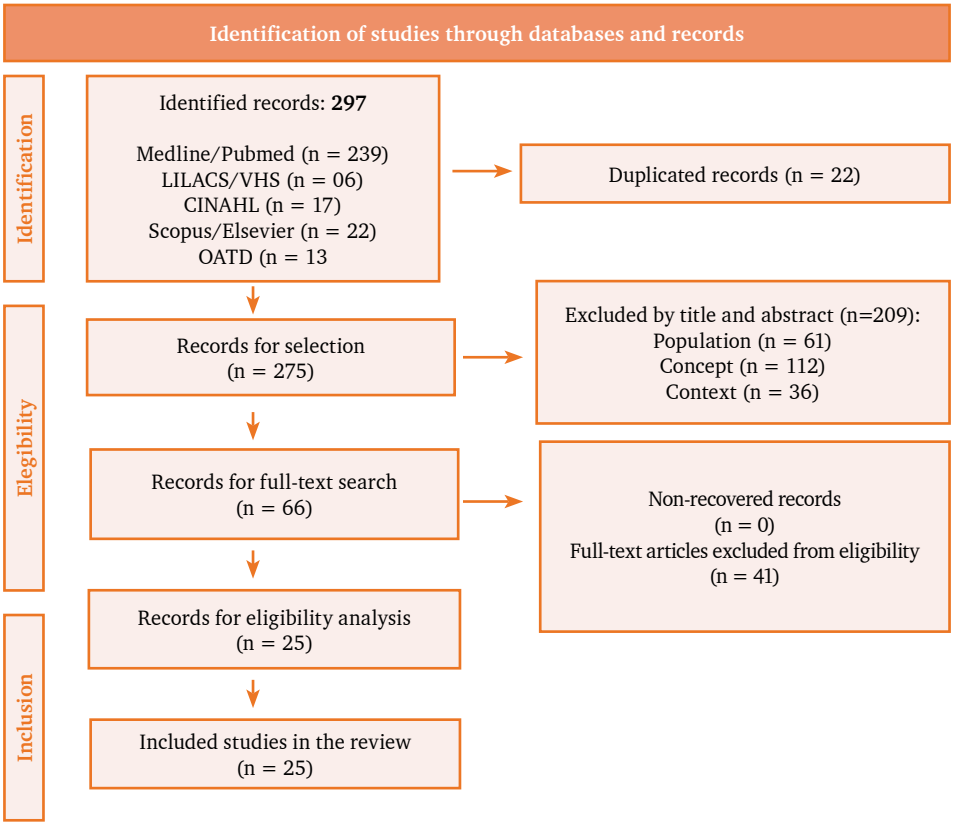
The studies were also grouped, relating the signs and symptoms of cardiotoxicity, type of cancer and antineoplastic drug involved (Table 3).

The research made it possible to identify the direct and indirect cardiovascular damage caused by cardiotoxic oncology therapy, which goes beyond the heart, affecting the entire cardiovascular and musculoskeletal system. These damages include changes in cardiac structure and function, myocardial oxygenation and risk of thrombosis, as well as ischemic and fatal electrocardiographic changes, fatal arrhythmias (such as atrial/ventricular fibrillation), dyspnea, chest pain, peripheral edema, weakness, reduced blood pressure, sudden death, palpitation, cardiorespiratory arrest, cardiogenic shock, reduced left ventricular ejection fraction, tachycardia and thrombosis. Based on a qualitative representation, the word cloud below summarizes the main signs and symptoms of cardiotoxicity identified in the included studies (Figure 2).

DISCUSSION

The 25 studies included exposed the cardiotoxic effects of different antineoplastic drugs administered at different dosages in patients with different types of cancer. During the qualitative synthesis of the studies, it was noticed that antineoplastic drugs generate signs and symptoms associated with changes in structure, function, cardiac oxygenation as well as thrombogenic changes. The most recent cardio-oncology guideline in the

Figure 1 - PRISMA-ScR flowchart



Source: prepared based on PRISMA-ScR recommendations[8]. Niterói, RJ, Brazil, 2023.

Table 2 - Summary of the characteristics of the included studies

Study / Author	Year / Country	Study design	Population			Antineoplastic drug	Signs and symptoms Cardiotoxicity
			n	Gender / Age range	Type of cancer		
E=1[9] Tjionas H, Gupta AK.	2017 USA	Case study	1	Woman 70 years	Multiple Myeloma	Carfilzomib	Dyspnea, bradycardia, atrioventricular block and severe heart failure
E=2[10] Grazziotin LR, Picon PD	2017 Brazil	Prospective multicenter study	109	Women 26-84 years	Breast	Trastuzumab	Cardiac insufficiency
E=3[11] Liu et al.	2017 China	Case study	1	Woman 62 years	Breast	Anthracycline	Severe mitral regurgitation and congestive cardiac failure
E=4[12] Watanabe H et al.	2017 Japan	Case study	1	Woman 78 years	Lung	Osimertinib	Dyspnea and congestive cardiac failure
E=5[13] Lampropoulos S et al.	2017 Grece	Case study	2	Men 65 and 49 years	Colorectal	Capecitabine	Acute myocardial infarction and cardiac arrest in asystole
E=6[14] Kwakman JJ et al.	2017 Netherlan-ds	Retrospective study	1973	Men/ Women >18 years	Metastatic colorectal	Capecitabine Oxaliplatin Bevacizumab	Ischemias, arrhythmias, chest pain, atrial fibrillation and congestive cardiac failure
E=7[15] Polk A et al.	2016 Denmark	Retrospective observational study	452	Women Average of 63 years	Breast	Capecitabine	Chest pain, dyspnea, palpitations, atrial fibrillation, ST segment changes, T wave and QTc prolongation, acute myocardial infarction and lethal cardiac arrest
E=8[16] Van Keerberghen CA et al.	2016 Belgium	Case study	1	Woman 46 years	Breast	Sinutinib	Hypotension, tachycardia, dyspnea, electrocardiogram with micro voltages and T wave inversion, elevated troponin I and severe congestive cardiac failure
E=9[17] Alici H et al.	2015 Turkey	Prospective cohort	51	Women Man Average of 51 years	Breast	Anthracycline Trastuzumab Cyclophospha-mide 5-FU Radiotherapy	Decrease in left ventricular ejection fraction, increase in transmitral flow velocity and significant decrease in the relationship between them
E=10[18] Jordan JH et al.	2014 USA	Longitudinal study	65	Men Women 5 1 ± 1 2 years	51 Breast 14 hematological	Anthracycline, Antimicrotubule Monoclonal Antibody	Decrease in left ventricular ejection fraction and myocardial injury
E=11[19] Khan MF et al.	2014 USA	Case study	1	Man 56 years	Pâncreas	Gencitabine	Congestive cardiac failure and left ventricular ejection fraction of 15 to 20% with hypokinesia
E=12[20] Y-Hassan S et al.	2013 Sweden	Case study	1	Man 55 years	Colorectal	Capecitabine	Takotsubo syndrome, cardiogenic shock, acute myocardial infarction and left ventricular dysfunction
E=13[21] Kim SM et al.	2012 Korea	Case study	1	Man 83 anos	Cólon	5-FU Leucovorin, Oxaliplatin	Takotsubo syndrome, cardiogenic shock, acute myocardial infarction and left ventricular dysfunction
E=14[22] Lestuzzi C et al	2010 Italy	Case study	1	Woman 47 anos	Metastatic breast	Capecitabine	Exertional angina and left ventricular ejection fraction of 55%
E=15[23] Farina A et al.	2009 Italy	Case study	1	Man 53 anos	Metastatic colon	Capecitabine	Chest pain and ST segment changes

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Table 2 - Summary of the characteristics of the included studies

Study / Author	Year / Country	Study design	Population			Antineoplastic drug	Signs and symptoms Cardiotoxicity
			n	Gender / Age range	Type of cancer		
E=17[25] Luján J et al.	2002 Spain	Case study	1	Man 69 years	Metastatic colon	Cisplatin 5-FU	Unstable angina, dyspnea and ST segment changes
E=18[26] Okumura H. et al.	2002 Japan	Cohort	13	Men Women 24-68 years	Acute leukemia	Daunorubicin	Congestive cardiac failure and elevation of BNP plasma levels
E=19[27] Meyer CC et al.	1997 USA	Cohort	483	Men Women Mean 60.9 ± 11.9 years	Distinct cancers	5-FU	Angina, tachycardia, hypotension, chest pain and sudden death
E=20[28] Keefe DL et al.	1993 USA	Case study	5	Men Women 47-68 years	Distinct cancers	5-FU	ST elevation and ventricular arrhythmias, acute myocardial infarction and cardiac arrest
E=21[29] Eskilsson J et al.	1988 Sweden	Cohort	76	Men Women Median 28-80 years	Distinct cancers	5-FU Cisplatin	Chest pain, change in ST segment, atrial and ventricular fibrillation
E=22[30] Landys K et al.	1985 Sweden	Cohort	42	Women 36-80 years	Breast	Mitoxantrone	Decrease in left ventricular ejection fraction
E=23[31] Sharifi R et al.	1985 USA	Randomized clinical trial	21	Men > 50 years	Prostate	Leuprolide Diethylestilbestrol	Fatal acute myocardial infarction, arrhythmia and venous thrombosis
E=24[32] Cornbleet MA et al.	1984 Netherlands	Prospective cohort	134	Women 28-80 years	Breast	Mitoxantrone	Electrographic changes, ST depression, inverted P wave and presence of multiple ectopic ventricles
E=25[33] Lahtinen R et al.	1982 Finland	Time series	37	Men Women 18-73 years	Distinct solid/ hematological cancers	Doxorubicin Daunorubicin	Drop in left ventricular ejection fraction, weakness, dyspnea, peripheral edema, angina, tachycardia and weakness

Source: The authors, Niterói, RJ, Brazil, 2023

world is Brazilian, published in 2020. It considers the diagnosis of cardiotoxicity based on the confirmation of a new cardiovascular change during or after antineoplastic treatment, whether of a clinical nature and/or change in biomarkers and/or in a cardiovascular imaging examination, with other etiologies having been excluded. It recommends that patients at cardiovascular risk receive follow-up according to specific follow-up protocols for each antineoplastic[34].

Among the antineoplastic drugs with a high potential for cardiotoxicity most cited in the included studies are 5-fluorouracil (5-FU), capecitabine (antimetabolic drugs), doxorubicin, daunorubicin (anthracyclines) and trastuzumab (monoclonal antibody). It was found that the antimetabolites, 5-FU and its prodrug, capecitabine, were extensively studied in 12 studies (48%). They are antineoplastics used in oncology for the treatment of solid cancers in the gastrointestinal, head and neck, esophagus, breast, liver, prostate, bladder and colorectal regions[34-35]. The signs and symptoms of antineoplastic drugs included relevant manifestations of cardiotoxicity, such as arrhythmias (atrial fibrillation, asystole, ventricular fibrillation and tachycardia), palpitations, shortness of breath, low blood pressure, chest pain and thrombosis. These signs and symptoms are associated with acute myocardial infarction (AMI), cardiorespiratory arrest, heart failure (HF), cardiogenic shock, sudden death and aortic stenosis[13,15,17,20,23,25,27-29].

The Guide of Conduct in Cardio-oncology (2018), attributes the symptoms of cardiotoxicity arising from

Table 3 – Grouping of studies regarding signs and symptoms of cardiotoxicity according to the type of cancer and antineoplastic drug

Studies	Signs and symptoms of cardiotoxicity	Type of cancer involved	Antineoplastic drug involved
E2[10], E3[11], E4[12], E9[17], E10[18], E11[19], E18[26], E19[27], E22[30],	Change in blood pressure Dyspnea Peripheral edema Weakness Reduction in LVEF Tachycardia Aortic stenosis	Acute → Leukemia Pancreas → Lung →	Anthracyclines Antimicrotubule Mitoxantrone Trastuzumab Gencitabine Osimertib
E5[13], E6[14], E7[15], E12[16], E13[21], E15[23], E17[25], E20[28], E21[29], E23[31],	Biomarker changes Ischemic and fatal electrographic changes Fatal arrhythmias (atrial/ventricular fibrillation) Chest pain Dyspnea Palpitation Thrombosis Cardiogenic shock CRA	Breast Colorectal → Distintive	Capecitabine and 5-FU, Mitoxantrone
E1[9], E8[16], E14[22], E16[24], E25[33]	Change in blood pressure Biomarker changes Ischemic and fatal electrographic changes Fatal arrhythmias (atrial/ventricular fibrillation) Pericardial effusion Dyspnea Chest pain Peripheral edema Elevated pulmonary pressure Reduction in LVEF Thrombosis	Breast and → Colorectal Kidney → Multiple → Myeloma Distinctive →	Sunitinib Capecitabine Sunitinib and Sorafenib Carfilzomib Anthracycline

Source: The authors, Niterói, RJ, Brazil, 2023

Figure 2 - Word cloud of signs and symptoms of cardiotoxicity identified in studies

Source: The authors, Niterói, Rio de Janeiro, Brazil, 2023

5-FU and capecitabine to the mechanism of coronary vasospasm. It highlights chest pain as the most common symptom, with a possible abrupt onset, from 3 hours to 5 days after the administration of 5-FU, and refers to progression to more serious cases such as cardiogenic shock, AMI, myocarditis, HF and sudden death. It considers a mortality rate of 2.2% to 13.3%[36]. This severity was also evidenced in studies E12[20], E19[27], E20[28] and E21[29], where patients developed cardiogenic shock, ventricular fibrillation, cardiorespiratory arrest and sudden death[20,27-29].

On the other hand, the Brazilian Cardio-oncology Guideline (2020), states that the mechanism by which these antineoplastics cause cardiac toxicity has not been completely defined, with hypotheses related to acute vessel spasm, direct toxicity to myocytes, endothelial dysfunction and a state of hypercoagulability, which can also cause thrombosis. The incidence rate of cardiotoxicity is 3.9% to 12.5%[34].

Regarding anthracyclines, which are commonly used in the treatment of acute leukemia, lymphoma, breast, thyroid and liver cancer, the included studies showed that patients present signs and symptoms of cardiotoxicity,

such as fatigue, weakness, peripheral edema, orthopnea, dyspnea exertion, tachycardia and chest pain. Furthermore, changes in biomarkers, left ventricular dysfunction and HF are observed[11,17,18,23,26]. The mechanisms involved in doxorubicin-induced cardiotoxicity are considered quite complex. A study published in 2020 deepened knowledge about oxidative stress, mitochondrial dysfunction and apoptosis, which play an important role in the development of cardiomyopathy. Doxorubicin disrupts the balance of mitochondria, resulting in damage[37].

There is a consensus in the literature regarding the dose-dependence and severity of cardiotoxicity caused by anthracyclines. The Brazilian Cardio-oncology Guideline (2020), highlights the importance of a maximum cumulative dose of doxorubicin of 400-550 mg/m^2. Diastolic dysfunction due to dose-dependent cumulative toxicity occurs at a cumulative dose of 200 mg/m^2, while systolic dysfunction occurs at doses above 400 mg/m^2[34]. Based on this context, the same guideline recommends a rigorous cardiovascular assessment and evaluation of the left ventricular ejection fraction (LVEF) before starting treatment with anthracyclines. Periodic monitoring with echocardiography (ECHO) is recommended with a normal baseline result, followed by ECHO after 3 months, 6 months and 1 year from the onset of treatment. If the baseline ECHO result is borderline (50-55%), troponin/NT-proBNP analysis should be performed within 72 hours after anthracycline administration and the ECHO should be repeated 3 months, 6 months and 1 year after the beginning of the treatment. If the baseline ECHO result reveals left ventricular dysfunction (<50%), it is necessary to perform troponin/NT-proBNP analysis within 72 hours after anthracycline administration and repeat the ECHO after 45 days, 6 months and 1 year after initiation of anthracycline treatment. Furthermore, the importance of including the analysis of biventricular systolic and diastolic function in the ECHO assessment stands out[34].

Regarding cardiac biomarkers, the E19 cohort followed 13 patients with acute leukemia using daunorubicin. It was found that 3 patients developed symptomatic HF and 5 patients developed subclinical HF during or after the end of treatment. In patients who did not develop HF, B-type natriuretic peptide (BNP) levels remained within the normal range. However, in patients with HF, the plasma BNP level increased above normal. It was concluded that the increase in plasma BNP levels preceded the manifestation of both clinical and subclinical HF, which indicates that BNP may be useful for the early diagnosis of anthracycline-induced cardiotoxicity[27].

Corroborating this cohort, the 2018 Guide of Conduct in Cardio-oncology recommends the early measurement of Troponins 0h, 24h and 72h after each cycle, and also the measurement of BNP (or NT-proBNP), for patients at high risk of cardiotoxicity. Furthermore, late measurement of troponins and BNP (or NT-proBNP) is recommended 1 month after the cycle, as well as measurement of natriuretic peptides for outpatient monitoring of cardiotoxicity due to anthracycline[35]. In addition to the various dysfunctions caused by anthracyclines when used alone, studies describe that combining previous or concomitant thoracic, mediastinal or breast radiotherapy, as well as treatment with trastuzumab, increases the risk of cardiotoxicity. This also occurs when there is a bolus infusion of anthracyclines[34].

Consolidating the context of this combination of therapies, a systematic review published in 2017, with patients undergoing breast cancer treatment using anthracycline associated with radiotherapy in the left breast region, showed a high probability of developing heart disease. It was identified that the cardiac dose increased the rate of major coronary events, including pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, coronary artery disease and, in rare cases, valvular disease[38].

With regard to the monoclonal antibody trastuzumab, used in the treatment of breast cancer, studies mainly reported a decrease in LVEF and HF[11,18,19]. In a study published in 2017, toxicity caused by changes in cardiac structure and function after trastuzumab infusion was also described. The participants, diagnosed with HER2+ breast cancer, presented changes in LVEF in 55% of cases and an increase in cardiac markers troponin T and troponin I, which led to the need to interrupt adjuvant treatment with trastuzumab[36].

According to a study published in 2019, trastuzumab targets the HER2 receptor, also known as ErbB2, which is overexpressed in approximately 20% of human breast cancers. Trastuzumab blocks heterodimerization between ErbB2 and ErbB3, thus affecting intracellular signaling and leading to the activation of apoptotic pathways and cell death. Furthermore, it can affect the heterodimerization between ErbB2 and ErbB4 in cardiac myocytes, resulting in contractile dysfunction[2].

Depending on the severity of cardiotoxicity, main guidelines recommend stopping trastuzumab treatment to allow recovery of cardiac function and a risk-benefit assessment to resume treatment. It is important to highlight that most cases of cardiotoxicity are reversible[5,34,36], however, recent studies suggest possible long-term effects related to fibrosis and the activation of

apoptotic pathways[2]. Furthermore, additional risk factors for the development of trastuzumab cardiotoxicity include renal dysfunction, excessive alcohol consumption, systemic hypertension, previous treatment with anthracycline and radiotherapy, and history of coronary artery disease[2,34].

Therefore, there is a consensus in the literature on the importance of evaluating cardiovascular function and cardiac care, which includes performing an ECG and echocardiogram, laboratory and biochemical tests, and measuring cardiac markers such as troponin I and NT pro-BNP[34, 35]. The Brazilian Cardio-Oncology Guideline (2020) details and recommends performing an ECHO before and every 3 months of treatment with trastuzumab and defines that in cases of borderline baseline ECHO (LVEF 50-55%) troponin/NT-proBNP should be measured up to 72 hours. In cases of baseline ECHO with LV dysfunction (<50%), HF must be treated, repeat ECHO every 3 months and measure troponin/NT-proBNP within 72 hours[34].

Given the severity and complexity of the signs and symptoms of cardiotoxicity, it is essential that healthcare professionals expand their knowledge about the antineoplastic drugs administered, the main toxic effects, the signs and symptoms and the possible worsening symptoms presented by cancer patients, in order to diagnose them early. cardiotoxicity and take measures to reduce cardiovascular damage.

A 2019 review highlights the importance of early diagnosis of the subclinical cardiotoxic effects of cancer therapies and highlights that the integrated approach by multidisciplinary cardio-oncology teams offers the best option for the prevention, diagnosis and treatment of cardiovascular diseases associated with cancer therapy[3].

The European Society of Cardio-Oncology recommends that cardio-oncology services be structured to address the prevention, detection, monitoring and treatment of cancer patients at risk of cardiotoxicity and/or with concomitant cardiovascular diseases. The importance of a multidisciplinary approach in these areas is highlighted to promote cardiovascular health and facilitate more effective oncological therapy[39].

Furthermore, the need to improve the recognition of the acute and chronic phases of cardiotoxicity for monitoring cancer patients is highlighted, which has not been clearly demonstrated in several types of cancer in recent years[40]. It is also necessary to improve the identification of patients at greatest risk of developing cardiotoxicity and establish guideline-directed screening recommendations[2].

Based on this scoping review, one can infer the need for rigorous cardio-oncological surveillance from the beginning of treatment, monitoring the cardiovascular structure, cardiac oxygenation, left ventricular ejection flow and the circulatory system during and after the cardiotoxic antineoplastic therapy, in order to early identify the signs and symptoms of cardiotoxicity.

Study limitations

Studies in languages other than English, Spanish and Portuguese were not considered, and although efforts were made to identify relevant studies for a comprehensive search, not all databases were used, which may result in the loss of some studies.

CONCLUSION

Mapping the signs and symptoms of cancer patients undergoing cardiotoxic antineoplastic therapy made it possible to identify direct and indirect cardiovascular damage, which can cause changes in cardiac structure and function, myocardial oxygenation and thrombogenesis. The main signs and symptoms of cardiotoxicity found were chest pain, decreased ejection fraction, heart failure, arrhythmias and dyspnea. The identification of cardiotoxicity is crucial for the evaluation and management of cancer patients. It is essential that healthcare professionals acquire knowledge in this area for early diagnosis or potential risk assessment.

It is important to highlight that more research is needed to better understand the mechanisms of action of antineoplastic therapies, their impact on the cardiovascular system, and to improve the identification of patients at greatest risk of developing cardiotoxicity. From this review, it will be possible to carry out new scientific studies that will contribute to the advancement of knowledge in the area, ensuring greater scientificity, evidence-based practice and safer care for cancer patients.

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