

Cardiotoxicity in cancer patients treated with chemotherapy: A systematic review

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ABSTRACT

Objective: The objective of the study was to assess the incidence of chemotherapy cardiotoxicity.

Methods: This is a systematic review carried out through the PubMed, VHL and Scientific Electronic Library Online databases, using the descriptors “Cardiotoxicity” and “Chemotherapy” associated with the Boolean operator “AND.” Initially, 15,090 articles were found between 2015 and 2021. After applying the defined inclusion and exclusion criteria, 80 studies remained, of which 27 underwent complete reading, after which all were included in the study.

Results: In total, 32,009 cancer patients were analyzed, of which 27,270 (85.2%) were female. Breast cancer was the most frequent neoplasm, with 11,145 (34.8%) cases. Regarding the type of chemotherapy, anthracycline was the most prevalent, analyzed in 18 (66.7%) studies, followed by trastuzumab, in 9 (33.3%) studies. Of the studies evaluated, five did not present any case of cardiotoxicity, a total of 2255 (8.3%) cases were recorded, in addition other outcomes mentioned in patients after chemotherapy were arrhythmia ($n = 522$), acute coronary syndrome ($n = 185$), diastolic dysfunction ($n = 184$), cardiomyopathy ($n = 161$), and arterial hypertension ($n = 89$).

Conclusion: Post-chemotherapeutic cardiotoxicity was mentioned in most studies, being present in a relevant percentage of the sample. Furthermore, these patients may develop other cardiovascular events.

Keywords: Cardiotoxicity, chemotherapy, oncology

Introduction

Chemotherapy cardiovascular involvement includes the development or exacerbation of cardiovascular diseases. In addition to cardiotoxicity, these patients are at increased risk of developing other cardiovascular complications, especially arrhythmias, ventricular dysfunction, systemic arterial hypertension, acute coronary syndrome, cardiomyopathy, and thromboembolic diseases.^[1-4] Anthracyclines and related compounds are among the chemotherapeutic agents most associated with the development of cardiotoxicity, in addition, to these other related drugs are alkylating agents

(cyclophosphamide), monoclonal antibodies (rituximab), protein kinase inhibitors, and HER2-targeted therapies (trastuzumab).^[1,4]

Chemotherapeutic cardiotoxicity can be defined as any functional and/or structural alteration of the cardiovascular system induced by cytotoxic antineoplastic drugs, being measured through the reduction of the left ventricular ejection fraction (LVEF), it can manifest in an acute, subacute, or chronic form.^[2,5] Cardiotoxicity represents one of the most significant adverse effects of this type of therapy. It is currently the second most common cause of morbidity and mortality in

patients with the previous cancer treatment, second only to oncological causes (recurrence or secondary neoplasms).^[3,4]

The appearance of chemotherapeutic cardiotoxicity may imply the interruption of chemotherapeutic treatment and, consequently, compromise the cure or adequate control of the neoplasm, in addition to the fact that heart failure may compromise the evolution of the case. It is also noteworthy that cardiotoxicity can be classified as type I, in which myocytes are affected by the toxic effects of drugs (e.g., those caused by anthracyclines) and suffer irreversible damage, and in type II, in which cardiac function is not compromised, is determined to be irreversible (such as that caused by trastuzumab).^[1,4,6,7]

This review seeks to assess chemotherapeutic cardiotoxicity, so that it is possible to analyze the epidemiological aspects related to this complication, such as risk factors, the most recurrent alterations and the most commonly associated antineoplastic drugs. Furthermore, it was also possible to assess the incidence of other cardiovascular complications resulting from the use of chemotherapy.

Methods

This is a systematic review that aims to assess the profile of chemotherapy cardiotoxicity cases. For this, searches were carried out in the Scientific Electronic Library Online, virtual health library and Medical Literature Analysis and Retrieval System Online (Medline/PubMed) databases using the descriptors “Cardiotoxicity” and “Chemotherapy,” in addition to of the Boolean operator “AND,” so that it was possible to maximize the number of studies found.

The inclusion criteria defined were original articles published between 2015 and 2021 in any language with descriptors

present in the title and/or abstract, while those that did not have content to achieve the proposed objective, in addition to a case report and case series, were excluded. Initially, 15,090 articles were found. Subsequently, the inclusion criteria were applied, excluding 15,010 articles [Figure 1].

After that, 80 studies were submitted for reading the title, of these 53 were selected for reading the title and abstract, of which 26 were excluded, leaving 27 studies for full reading. Then, all 27 articles were included to compose the database of this review, as they contained enough data to achieve the proposed objective. For data extraction, the Microsoft Office Excel®8 program was used to store and tabulate the data obtained.

The Kappa index was used to assess the agreement of the evaluators in the selection of articles. The value 0.8978 was obtained, which, according to Landis and Koch⁹, suggests excellent reliability, since the closer the value to 1, the greater the agreement of the reviewers. Therefore, it was possible to proceed with the systematic review [Table 1].

Results

In Table 2, it is possible to analyze that only 2 (7.4%) studies had an impact factor lower than 1.02. With regard to the study

Table 1: Kappa index

Indexes	Category 1*	Category 2**
Category kappa	0.8978	0.8978
Category kappa standard error	0.0457	0.0455
Category kappa 95% confidence interval	Sup: 0.8082 Inf: 0.8087	Sup: 0.9874 Inf: 0.9868

*Articles included in the study **Articles excluded from the study. Source: survey data, 2021

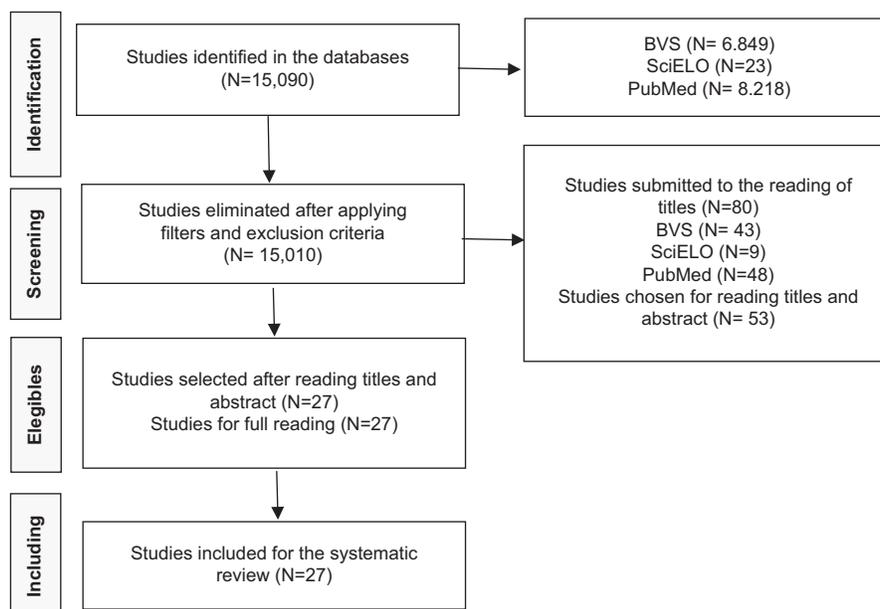


Figure 1: Study PRISMA flow diagram. Source: survey data, 2021

Table 2: Characteristics of the studies selected for review

Authors	Journal (Qualis)	Type of Study	Study Location	Sample (n)
Alam <i>et al.</i> ^[10]	Indian Heart J IF: 1.36	Prospective single center	Índia	108
Aula <i>et al.</i> ^[11]	Anticancer Res IF: 1.994	Prospective single center	Finlândia	45
Baech <i>et al.</i> ^[12]	Br J Haematol IF: 6.998	National Cohort	Dinamarca	2.440
Ballesteros <i>et al.</i> ^[13]	Colomb Med IF: 0.164	Prospective	Colômbia	113
Barros <i>et al.</i> ^[14]	Arch Bras Cardiol IF: 1.02	Prospective cohort	Brasil	112
Cavalcanti <i>et al.</i> ^[15]	Ars Pharmaceutica IF: 0.4	Observational	Brasil	24
Coutinho <i>et al.</i> ^[16]	Clin Res Cardiol. IF: 4.455	Observational	Portugal	105
Choe <i>et al.</i> ^[17]	Clin Cardiol. IF: 2.248	Prospective single center	Coreia do Sul	273
Chang <i>et al.</i> ^[18]	ESC Heart Fail. IF: 3.902	Retrospective cohort	Taiwan	386
Dyhl-Polk <i>et al.</i> ^[19]	Oncologist IF: 5.025	Prospective	Dinamarca	108
Franchi <i>et al.</i> ^[20]	Oncologist IF: 5.025	Cohort	Itália	6.728
Ho <i>et al.</i> ^[21]	J Chin Med Assoc IF: 2.17	Retrospective cohort	Taiwan (Ásia)	3.781
Kitayama <i>et al.</i> ^[22]	Breast Cancer IF: 4.239	Prospective	Japão	40
Lee <i>et al.</i> ^[23]	Strahlenther Onkol. IF: 3.621	Retrospective	Taiwan (Ásia)	1.730
Mizia-Stec <i>et al.</i> ^[24]	Med Oncol. IF: 3.064	Prospective multicentric	-	67
Olivieri <i>et al.</i> ^[25]	Oncologist IF: 5.025	Prospective	Itália	99
Peng <i>et al.</i> ^[26]	Cancer Common IF: 6.162	Prospective	China	527
Portugal <i>et al.</i> ^[28]	Rev Port Cardiol. IF: 0.96	Prospective	Portugal	158
Ruiz-Mori <i>et al.</i> ^[27]	Horiz. Med. IF: 2.67	Retrospective	Peru	985
Samosir <i>et al.</i> ^[29]	APJCP IF: 2.06	Retrospective	Indonésia	49
Sandamali <i>et al.</i> ^[30]	Biomed Res Int IF: 3.411	Prospective cohort	Índia	196
Shah <i>et al.</i> ^[31]	Cardiovasc Toxicol. IF: 3.231	Retrospective	EUA (Flórida)	99
Shamai <i>et al.</i> ^[32]	BMC Cancer IF: 4.4	Observational	Israel	43
Tang <i>et al.</i> ^[33]	Medicine IF: 1.552	Observational	China	62
Tzolos <i>et al.</i> ^[34]	Clin Oncol IF: 4.126	Multicentric cohort	-	78
Upshaw <i>et al.</i> ^[35]	JACC Cardiovasc Imaging IF: 14.805	Longitudinal cohort	EUA (Filadélfia)	362
Wittayanukorn <i>et al.</i> ^[36]	J Oncol Pharm Pract IF: 1.52	Observational	EUA	937

IF: impact factor, USA: United States of America. Source: survey data, 2021

location, a heterogeneous distribution is noted, with the United States being the country with the most number of studies, totaling 3 (11.1%). Furthermore, regarding the number of cancer patients analyzed, there were a total of 32,009 cases.

From Table 3, it is observed that most of the patients analyzed were female, in which there were 27,270 (85.2%) cases, while there were 4533 (14.2%) of males, with 12 studies not included males in the sample. Breast cancer was the most frequent neoplasm, with 11,145 (34.8%) cases, followed by colorectal cancer, with 3925 (12.3%). Other reported neoplasms were lymphoma, leukemia, osteosarcoma, and sarcoma.

Some studies did not mention the presence of comorbidities in the sample, when analyzing this variable, cardiovascular risk was reported in 2489 (9.1%) patients, arterial hypertension in 1509 (5.5%), and diabetes mellitus in 777 (2.8%). Other comorbidities mentioned in the studies were current smoking, hyperlipidemia, chronic kidney disease, and obesity.

Regarding the type of chemotherapy, anthracycline was the most prevalent, analyzed in 18 (66.7%) studies, followed by trastuzumab, in 9 (33.3%) studies.

When analyzing the presence of cardiotoxicity in the analyzed patients, five studies did not present any case. In total, 2,255 (8.3%) cases of cardiotoxicity were recorded, and the study by Wittayanukorn *et al.*^[36] had only cases of cardiotoxicity in its sample, and the causes were later evaluated. In addition to cardiotoxicity, other outcomes were evaluated, such as the development of arrhythmia ($n = 522$), acute coronary syndrome ($n = 185$), diastolic dysfunction ($n = 184$), cardiomyopathy ($n = 161$), and arterial hypertension ($n = 89$) after chemotherapy [Table 4].

Regarding the risk factors for the development of cardiotoxicity, only nine studies evaluated this, and the presence of arterial hypertension was mentioned by three studies, being the most cited factor. From Table 4, it can be observed that there were

Table 3: Characteristics of the sample of studies included in the review

Article	Age (years)	Male Female	CMT	Cancer type	Comorbidity
Alam <i>et al.</i> ^[10]	Avarage: 44,17	6 40	Doxorubicin (Anthracycline): 46	Mama: 40 Osteosarcoma: 3 Others: 3	SAH: 5
Aula <i>et al.</i> ^[11]	Avarage: 11	26 19	Anthracycline: 45	-	-
Baech <i>et al.</i> ^[12]	-	1.271 1.169	Anthracycline or R-CHOEP: 1994	Lymphoma: 2,440	-
Ballesteros <i>et al.</i> ^[13]	Avarage: 6,35	68 45	Antraciclina: 113	Leukemia: 78	-
Barros <i>et al.</i> ^[14]	Avarage: 51,4	1 111	AGIR: 90 AntiHER2: 29 Others: 20	Mama: 112	SAH: 39 DM: 8 HLP: 21 SMK: 25
Cavalcanti <i>et al.</i> ^[15]	Avarage: 51,4	0 24 (100)	Anthracycline: 21 Fluorouracil: 10 Cyclophosphamide: 10 Taxane: 16 Trastuzumab: 24	Mama: 24	SAH: 6 DM: 2
Cruz <i>et al.</i> ^[38]	-	0 105	Anthracycline: 105	Mama: 105	-
Choe <i>et al.</i> ^[17]	Avarage: 53,9	0 273	Trastuzumab: 273 Anthracycline: 212 Taxane: 159 Fluorouracil: 18	Mama: 273	SAH: 69 DM: 28 HLP: 61 SMK: 7
Chang <i>et al.</i> ^[18]	Median: 54	0 386	Trastuzumab: 386 Anthracycline: 187 Cyclophosphamide: 104 Fluorouracil: 68 Taxane: 199	Mama: 386	DRC: 19 VC: 10 SMK: 11 DRC: 19
Dyhl-Polk <i>et al.</i> ^[19]	Median: 66	59 49	Fluorouracil: 18	Colorectal: 82 Anal: 26	SAH: 35 HLP: 73 DM: 6 SMK: 16 Obesity: 16
Franchi <i>et al.</i> ^[20]	Avarage: 55	0 19.144	Trastuzumab: 6.728	Mama: 6.728	CV risk: 2.489
Ho <i>et al.</i> ^[21]	Avarage: 64,5	2164 1617	-	Colorectal: 3781	SAH: 743 DM: 460 CKD: 170 HLP: 280 SMK: 121
Kitayama <i>et al.</i> ^[22]	Avarage: 55	0 40	Trastuzumab: 18 Anthracycline: 34 Taxane: 33	Mama: 40	SAH: 7 DM: 2 HLP: 14 SMK: 12 CKD: 1 Obesity: 5
Lee <i>et al.</i> ^[23]	Avarage: 50,3	0 1730	Anthracycline: 1730	Mama: 1730	SAH: 294 DM: 104 TIA: 14 IS: 6
Mizia-Stec <i>et al.</i> ^[24]	-	30 37	Trastuzumab: 273 Anthracycline: 58 Rituximab: 50	Non-Hodgkin's Lymphoma: 67	SAH: 28 DM: 9 SMK: 30 IS: 2
Olivieri <i>et al.</i> ^[25]	Avarage: 60	56 43	Anthracycline: 99	Lymphoma: 99	SAH: 29 DM: 6 Obesity: 5 HLP: 18 SMK: 28

(Contd...)

Table 3: (Continued)

Article	Age (years)	Male Female	CMT	Cancer type	Comorbidity
Peng <i>et al.</i> ^[26]	Avarage: 57	348 179	Fluorouracil: 196 Capecitabine: 331	-	SAH: 106 DM: 29 DCV: 13 HLP: 4
Portugal <i>et al.</i> ^[28]	Avarage: 54,6	0 158	Anthracycline with or without trastuzumab: 158	Mama: 158	-
Ruiz-Mori <i>et al.</i> ^[27]	-	381 602	-	-	-
Samosir <i>et al.</i> ^[29]	Avarage: 9,18	31 18	Daunorubicin (Anthracycline): 49	Leukemia: 49	-
Sandamali <i>et al.</i> ^[30]	Avarage: 53,6	0 196	Anthracycline: 196	Mama: 196	DM: 84 HLP: 39
Shah <i>et al.</i> ^[31]	Median: 64	48 51	-	Hematology: 78	-
Shamai <i>et al.</i> ^[32]	Avarage: 58	0 26	Anthracycline: 43	Sarcoma: 43	SAH: 16 HLP: 8 SMK: 11
Tang <i>et al.</i> ^[33]	-	22 40	Cetuximab: 62	Colorectal: 62	-
Tzolos <i>et al.</i> ^[34]	Median: 52	0 78	Epirubicin (Anthracycline)	Mama: 78	SAH: 17 DM: 6 SMK: 13
Upshaw <i>et al.</i> ^[35]	Median: 49	0 362	Doxorubicin: 219 Trastuzumab: 83 Combination: 60	Mama: 362	SAH: 115 DM: 33 SMK: 25 HLP: 76
Wittayanukorn <i>et al.</i> ^[36]	Avarage: 51,1 e 62,2	22 828	Transtuzumab: 685 Bevacizumab: 167 Lapatinib: 150 Pertuzumab: 12 Everolimus: 4	Mama: 937	-

CMT: Chemotherapy. Male: Male. Female: Female, SAH: Systemic arterial hypertension, DM: Diabetes mellitus, HLP: Hyperlipidemia, SMK: Smoking, TIA: Transient ischemic attack, IS: Ischemic stroke, CAD: Coronary artery disease, CV: Cardiovascular, CKD: Chronic kidney disease. Source: survey data, 2021

16 deaths from cardiovascular causes, two of these cases were due to cardiotoxicity.

Discussion

This review showed a higher prevalence of female patients in the analyzed studies, with breast cancer and colorectal cancer being, respectively, the most prevalent in the sample. Likewise, chemotherapy with anthracycline combined or not with trastuzumab was the most frequent. In fact, breast cancer is currently the most commonly diagnosed malignancy in the world, followed by lung cancer and colorectal cancer, respectively.^[37]

Anthracyclines are antineoplastic agents commonly used in adjuvant or neoadjuvant therapy, as well as in the treatment of metastases. This class of drugs, represented by doxorubicin, epirubicin and others, forms a complex with DNA, inhibiting the synthesis of nucleic acids and proteins, through cleavage by topoisomerase II, which results in its cytotoxic activity. The mechanisms of cardiotoxicity described for this class involve lipid peroxidation, oxidative stress, apoptosis and necrosis

of cardiac cells, in addition to the impairment of proteins and transcription factors relevant to the heart, resulting in a negative balance of sarcomeric proteins and an imbalance in cardiac function.^[1,3,38]

In the study, it was possible to observe the presence of cardiovascular risk factors in cancer patients, such as systemic arterial hypertension, diabetes mellitus, smoking, hyperlipidemia, obesity, and chronic kidney disease. In addition to these, it is known that other factors such as inflammatory diseases, chronic obstructive pulmonary disease, and the presence of cancer are associated with high cardiovascular risk.^[39] Therefore, care with the identification and control of cardiovascular risk factors should be redoubled in patients undergoing chemotherapy with potential for cardiotoxicity.^[40,41]

Cardiotoxicity was recorded in 8.3% of cancer patients who underwent chemotherapy, similar to the study by Volkova and Russell^[42] observed that anthracycline can induce heart failure in up to 8.7% of cases, while Curigliano *et al.*^[43] reported that in patients treated with trastuzumab the cardiotoxicity is up to 3.8% and with cyclophosphamide it varies between 7 and

Table 4: Cardiotoxicity and related factors

Article	Cardiotoxicity	Cardiotoxicity predictors	Other outcomes
Alam <i>et al.</i> ^[10]	no case	-	-
Aula <i>et al.</i> ^[11]	no case	-	Myocardial ischemia: 36 ACS: 6
Baech <i>et al.</i> ^[12]	108	-	CV disease: 243
Ballesteros <i>et al.</i> ^[13]	20	SAH Pulmonary hypertension Global longitudinal myocardial deformation	SAH: 14 ECG abnormality 65 Pulmonary hypertension 17 Pericardial effusion: 14 Valve insufficiency: 7
Barros <i>et al.</i> ^[14]	18	EV contractile change LV systolic dysfunction Global longitudinal strain	Segmental movement of the LV wall
Cavalcanti <i>et al.</i> ^[15]	3	-	PTE: 1
Cruz <i>et al.</i> ^[38]	24	-	-
Choe <i>et al.</i> ^[17]	27	-	-
Chang <i>et al.</i> ^[18]	5	-	CV and Cerebrovascular: 21 Death CV: 12 IS: 4
Dyhl-Polk <i>et al.</i> ^[19]	no case	-	ACS: 6 Arrhythmia: 2
Franchi <i>et al.</i> ^[20]	54	-	CV changes: 109 Cardiomyopathy: 161
Ho <i>et al.</i> ^[21]	556	SAH; CKD; Advanced age	-
Kitayama <i>et al.</i> ^[22]	4	-	-
Lee <i>et al.</i> ^[23]	82	-	CAD: 167
Mizia-Stec <i>et al.</i> ^[24]	10	-	-
Olivieri <i>et al.</i> ^[25]	2	-	-
Peng <i>et al.</i> ^[26]	161	SAH; CMT with capecitabine duration of treatment preexisting heart disease	Arrhythmia: 110 Ischemia change: 105 IS: 6
Portugal <i>et al.</i> ^[28]	30	Immunotherapy GLS Decrease	-
Ruiz-Mori <i>et al.</i> ^[27]	48	-	Arrhythmia: 406 SAH: 75 Angina: 184 DVT: 26 Pericardial effusion: 143 Others: 103
Samosir <i>et al.</i> ^[29]	5	Age ≥ 4 years Dose	FEVE Reduction: 33
Sandamali <i>et al.</i> ^[30]	65 (subclinical)	Obesity Chest wall radiation	-
Shah <i>et al.</i> ^[31]	29	History of PTE/DVT Karnofsky performance status $>80\%$	Death from disease CV 2
Shamai <i>et al.</i> ^[32]	6	-	Death from cardiotoxicity: 2
Tang <i>et al.</i> ^[33]	no case	-	Arrhythmia: 4 ECG changes 27 Chest pain: 1
Tzolos <i>et al.</i> ^[34]	no case	-	Myocardial injury assessed by troponin 45
Upshaw <i>et al.</i> ^[35]	61	Smoking; E/e' ratio Afro American race	Diastolic dysfunction: 184
Wittayanukorn <i>et al.</i> ^[36]	937	-	-

LV: Left Ventricle, PTE: Pulmonary thromboembolism, CAD: Coronary artery disease, CV: Cardiovascular, CMT: Chemotherapy, AMI: Acute myocardial infarction, DVT: Deep vein thrombosis, LVEF: Ventricular ejection fraction, CKD: Chronic kidney disease, IS: Ischemic stroke, ACS: Acute coronary syndrome, ECG: Electrocardiogram. Fonte: dados da pesquisa, 2021

28%. The increased risk for the development of cardiotoxicity associated with the use of anthracyclines is related to younger

patients, the female sex, the rapid rate of drug infusion, the high cumulative dose, and the presence of hypocalcemia,

hypomagnesemia, and previous cardiovascular diseases, such as coronary heart disease and hypertension.^[40] Consistent with these facts, this study found risk factors associated with chemotherapy cardiotoxicity, such as the presence of systemic arterial hypertension.

The study by Wittayanukorn *et al.*^[36] evaluated reports of chemotherapy-related cardiotoxicity in breast cancer patients in the United States, identifying 937 cases. The most prevalent drug was trastuzumab in combination with doxorubicin or cyclophosphamide, with 25% of the total reports being associated with death or disability. Such findings are in agreement with the study by Chen *et al.*,^[44] which presents evidence demonstrating that the use of anthracyclines with trastuzumab increases the risk of heart failure, while the study by Seidman *et al.*^[45] demonstrates an association of the use of anthracyclines with cyclophosphamide and trastuzumab with the incidence of dysfunction heart. In addition to these outcomes, this review also demonstrates the occurrence of arrhythmias, acute coronary syndrome and cardiomyopathy in patients undergoing chemotherapy, evidencing the existing cardiovascular risk.

In view of all these factors discussed, it is important to reaffirm the need to know the cardiotoxic effects of chemotherapy, as well as the cardiovascular risk that the patient presents, so that the likelihood of poor treatment outcomes is combated. In addition, the cardiovascular risks and cardiotoxicity demonstrated in this work may help the surveillance of adverse events in cancer patients undergoing chemotherapy, as well as guide future studies.

Conclusions

Cardiotoxicity was highlighted as relevant in most studies, presenting a percentage of review cases in this review, in addition to cardiovascular manifestations such as coronary syndrome and systemic arterial hypertension from chemotherapy. Finally, regarding the types of chemotherapy, the most prevalent was anthracycline followed by trastuzumab.

Conflict of Interest

Nothing to declare.

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None.

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