

Cardiovascular Diseases in Oncological Patients Treated at a Tertiary Hospital in the Northern Macroregion of Rio Grande do Sul

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Abstract

Background: Cancers (CAs) are related to cardiovascular diseases (CVDs), mainly due to the cardiotoxicity of oncological therapies (OTs).

Objectives: Analyze and describe the CVDs that affect oncological patients (OPs) before and after the diagnosis of CA.

Methods: This is a retrospective cohort study carried out with OPs from a Tertiary Hospital in the Northern Macroregion of Rio Grande do Sul, in which data was obtained from medical records dated between 2011 and 2020, which were analyzed using statistical techniques, mainly with the objective of determining the prevalence, incidence, and factors associated with CVDs.

Results: The sample included 250 OPs distributed over 10 years. Regarding CVDs, prevalence and incidence were, respectively, 47.6% and 13.6%. It was noted the predominance, in the previous conditions, of systemic arterial hypertension (67.7%) and, in the incident disorders, of deep vein thrombosis (30.6%). The total incidence was associated with male sex ($p=0.003$), smoking ($p=0.023$) and metabolic ($p=0.025$) and pulmonary ($p=0.047$) comorbidities. The incidence after the start of OT was linked to radiotherapy ($p=0.015$) and chemotherapy ($p=0.011$), in particular, fluorouracil ($p=0.025$) and oxaliplatin ($p=0.033$).

Conclusions: The relationship between CAs and CVDs has become clear, highlighting the importance of promoting the progress of cardio-oncology, especially with the aim of providing better therapeutic perspectives for OPs.

Keywords: Cardiotoxicity; Radiation injuries; Chemically-induced disorders.

Introduction

In several countries, population aging has become clear, mainly due to the decrease in the fertility rate and the increase in life expectancy.¹ This panorama had a significant impact on the health of the population, considering that the elderly often have a higher global burden of diseases.² In this way, a rise in cardiovascular diseases (CVDs) and cancers (CAs) could be noted, standing out in the context of chronic non-communicable diseases.³

At the same time, there was an evolution in medical sciences, which resulted in a decline in mortality rates from the conditions mentioned above.^{4,5} In view of this, for example, an increase in the survival of oncological patients (OPs) was observed, who began to be more frequently affected by CVDs.⁶ Faced with this situation, such disorders highlighted the existence of unexplored pathophysiological relationships, which supported the development of new scientific works.

Therefore, it was possible to recognize that the elucidated diseases interact mainly due to shared risk factors, the impact of malignancy on the cardiovascular system, and the cardiotoxicity of oncological therapies (OTs).⁷ In this reality, cardio-oncology was designed, that is, a multidisciplinary field focused on understanding cardiotoxic mechanisms, preventing, detecting, and managing cardiovascular repercussions, and enhancing therapeutic interventions.⁸

However, it is important to highlight that there is still a significant gap in scientific production in the cardio-oncological sphere compared to other medical specialties. This is largely due to the delay in the development of studies focused on the topic, which can be exemplified by the circumstance that the first report of CVD associated with OT was only published in 1967.⁹

Given the information presented, the research in explanation was established, with the purpose of expanding and disseminating knowledge linked to the cardio-oncological domain, specifically through the investigation of CVDs that affected the OPs of a Tertiary Hospital in the Northern Macroregion of Rio Grande do Sul.

Methods

This is a retrospective cohort study carried out at the Hospital de Clínicas de Passo Fundo, in Rio Grande do Sul,

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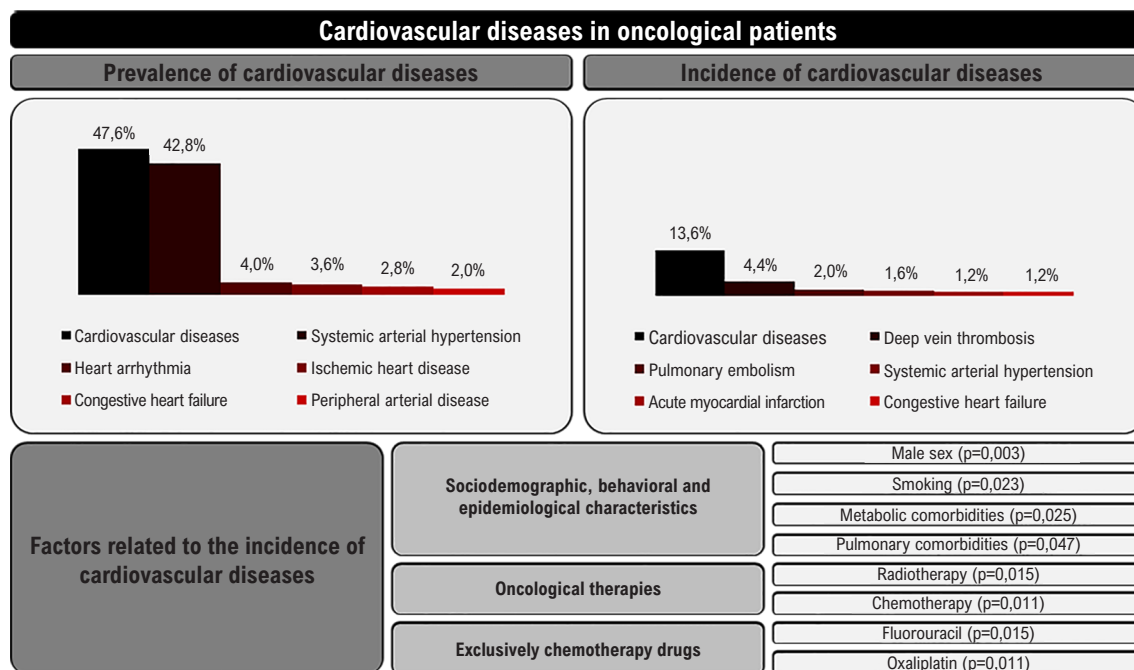
Manuscript received September 15, 2023, revised manuscript November 16, 2023, accepted November 17, 2023

DOI: <https://doi.org/10.36660/abchf.20230081>

Central Illustration: Cardiovascular Diseases in Oncological Patients treated at a Tertiary Hospital in the Northern Macroregion of Rio Grande do Sul



ABC Heart Failure & Cardiomyopathy



ABC Heart Fail Cardiomyop. 2023; 3(3):e20230081

Central Illustration - Cardiovascular diseases in oncological patients. Source: Own (2023).

between August 2022 and July 2023, with the objective of analyzing and describing CVDs developed before and after the diagnosis of CA by OPs treated between January 2011 and December 2020.

In the interval in question, a total of 5392 OPs were identified. Given this, it became imperative to determine the appropriate sample size for the research. Therefore, the OpenEpi v3.01 software (free distribution) was used, considering a CVD rate in the population of 20%, a sampling error of 5%, and a confidence interval of 95%, which resulted in a set of 246 OPs, which was adjusted to 250 OPs due to the possibility of loss of information.

In parallel, a simple probabilistic sampling was defined, and, using the LibreOffice Calc v7.6.0 software (free distribution), a random selection algorithm was applied to the sample contingent, which culminated in an ordered list of 500 OPs. Then, a collection was established through the analysis of medical records, aiming to reach a sample of 250 OPs randomly distributed over 10 years.

It is important to emphasize that individuals of both sexes and all age groups who were diagnosed with at least one type of CA were included in accordance with Classes C00-C96 of Chapter II of the 10th Revision of the International Classification of Diseases. In this context, it is worth highlighting that the exclusion was directed at those who had incomplete histories and/or incorrect diagnoses.

From the medical records, priority was given to extracting the variables: sex (female or male); age (< 60 years or ≥ 60 years); skin color (white or non-white); macroregion (north or non-north); smoking (smoking or non-smoking); comorbidities (cardiovascular, metabolic and pulmonary); CAs (nomenclature, staging, follow-up, and outcome); exposure to OTs (modality, protocol and start and end dates); and incidence of CVDs (description and date of diagnosis).

Sequentially, the information obtained was double entered and processed in the EpiData v3.1 software (free distribution), and after that, statistical analysis was conducted in the PSPP v2.0.0 software (free distribution). At this stage, the purpose was to characterize the OPs based on the absolute and relative frequencies of qualitative variables and measures of dispersion and central tendency of quantitative variables; detail CVDs through prevalence and incidence rates; and identify the factors associated with CVDs, using Pearson's Chi-Square Test and Fischer's Exact Test, approaching a significance level of 5%.

Ultimately, it is important to note that the scientific production highlighted constitutes an excerpt from the project entitled "Prevalence of Neoplasms in the Rural Population and Associated Factors", which was submitted to the Ethics Committee in Research with Human Beings of the Universidade Federal da Fronteira Sul, being approved by Opinion No. 5,180,104, which complies with Resolution 466/12 of the National Health Council.

Results

It was necessary to analyze 397 medical records to include a sample of 250 OPs. In this overview, it is necessary to mention that 147 OPs were removed according to the exclusion criteria. Furthermore, it is worth noting that 103 OPs were discarded due to the interruption of collection after obtaining the sample size. For a better understanding, such information was integrated and sequenced in Figure 1.

Among the validated OPs, it was noted that 55.6% were male sex, 54.0% were aged ≥ 60 years, 96.8% had white skin color, and 98.8% were from the Northern Macroregion of Rio Grande do Sul. Regarding CAs, it was found that 57.6% were diagnosed between 2011 and 2015, while 42.4% were discovered between 2016 and 2020. In this circumstance, there was a predominance of CAs of the breast (14.0%), prostate (10.8%), rectum (7.6%), kidney (6.8%), and non-melanoma skin (6.4%).

During the exploratory analysis, it was found that 119 OPs had pre-existing CVDs, which determined a total prevalence of 47.6%. In this context, a total of 158 CVDs were observed, with emphasis on systemic arterial hypertension (SAH; 67.7%), heart arrhythmia (HA; 6.3%), ischemic heart disease (IHD; 5.7%), congestive heart failure (CHF; 4.4%), and peripheral arterial disease (PAD; 3.2%). It is worth pointing out that these CVDs had, respectively, specific prevalences of 42.8%, 4.0%, 3.6%, 2.8%, and 2.0%.

In general, research considers SAH as a cardiovascular risk factor (CRF) instead of CVD, mainly due to its chronic nature. Because of this, a particular analysis of CVDs was carried out, excluding SAH. As a result, 42 OPs were affected, which defined a prevalence of 16.8%. It is important to emphasize that the decision was made to present the prevalence with and without SAH, as this disorder would be addressed in diagnoses subsequent to CA.

In addition, it was possible to verify that 34 OPs developed CVD after CA, defining a total incidence of 13.6%. In this panorama, there were a total of 36 CVDs, of which deep vein thrombosis (DVT; 30.6%), pulmonary embolism (PE; 13.9%), SAH (11.1%), acute myocardial infarction (AMI; 8.3%) and CHF (8.3%) were the most frequent. It should be noted that these CVDs included, respectively, specific incidences of 4.4%, 2.0%, 1.6%, 1.2% and 1.2%.

Based on this information, the aim was to identify the sociodemographic, behavioral, and epidemiological characteristics data of the OPs that were related to the incidence of CVDs. Thus, it became clear that there were statistically significant differences regarding male sex, smoking, and metabolic and pulmonary comorbidities, as indicated in Table 1.

Additionally, a temporal perspective was established based on the difference between the OT start dates and CVD diagnosis dates for the 34 OPs with incident CVDs. Therefore, it was found that 1 OP demonstrated an interval of -2.7 months, which indicated a CVD prior to OT, which was investigated and revealed, as an exception, a pathogenesis linked to pericardial metastasis.

In this scenario, it was concluded that 33 OPs developed CVDs after the start of OT. Therefore, it was found that the time until the diagnosis of CVD was, on average, 26.8 months (± 29.2 ; 0.6-95.3). From this, the aim was to elucidate the OTs related to the incidence of CVDs. Consequently, statistical significance was evidenced for submission to radiotherapy (RT) and chemotherapy (CT), which can be seen in Table 2.

Considering that CT exhibited a value of $p < 0.05$, the investigation of exclusively chemotherapy drugs (ECDs) was deepened, with the purpose of exploring the association with the incidence of CVDs. From this perspective, it was

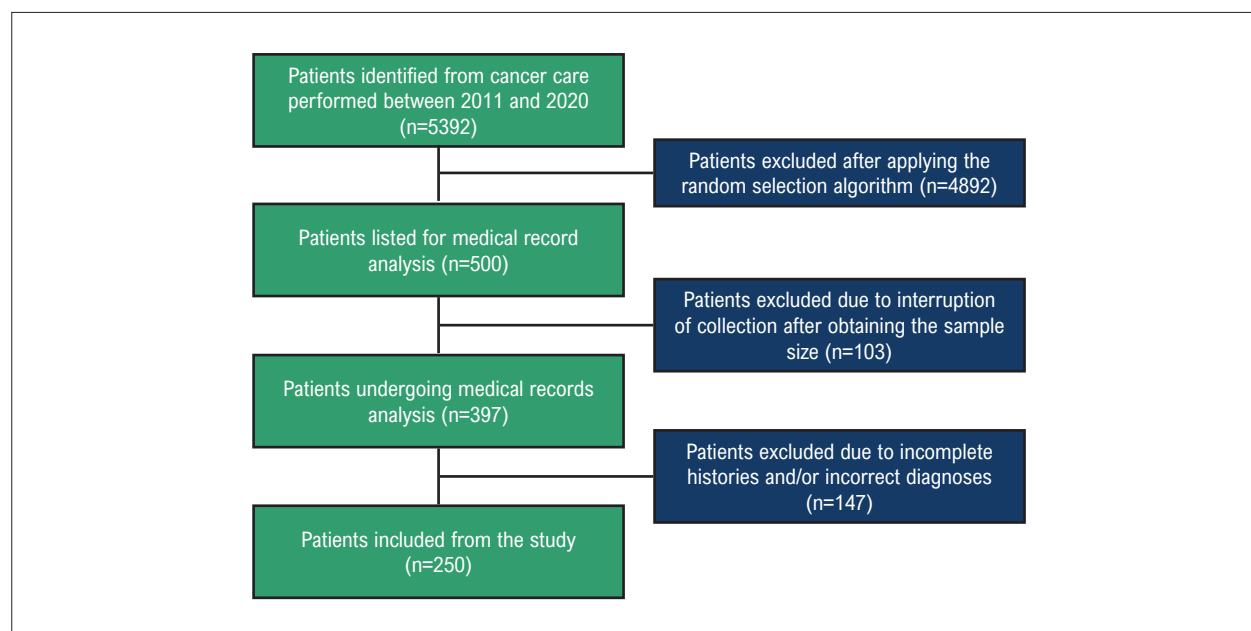


Figure 1 – Sample selection flowchart. Source: Own (2023).

possible to identify significant results regarding fluorouracil and oxaliplatin, as shown in Table 3. It is worth highlighting that these substances represented 31.3% of ECDs and 23.8% of all antineoplastic drugs (ADs) administered in this subsample of OPs.

Finally, it is important to know that, in order to elucidate the analysis in question, the most pertinent results were reorganized and presented in the Central Illustration.

Discussion

The study described revealed a total prevalence of CVD of 47.6% in OPs, which was higher than scientific references. For example, Youn et al. and Battisti et al. reported, respectively, previous CVDs in 11.3% and 16.2% of OPs.^{10,11} Therefore, it is worth pointing out that the discrepancy in relation to the result obtained arises from the inclusion of SAH in the current analysis, which was addressed as FRC in the studies elucidated. Given this, the calculation excluding SAH was emphasized, which resulted in a rate of 16.8%, which approached the upper limit of the range in question.

In the research in evidence, the predominance of SAH was noted, with a specific prevalence of 42.8%. This condition was followed by HA, IHD, CHF, and PAD, which manifested, respectively, rates of 4.0%, 3.6%, 2.8%, and 2.0%.

In reference to SAH, Paterson et al. described a prevalence of 31.7% in OPs.¹² Even though it showed a considerable percentage, the value displayed was lower than that obtained in the current assessment. This difference may be linked to the predominance of individuals aged ≥ 60 years in the current research since this parameter is associated with the elucidated disease, especially due to arterial stiffening.¹³

In the scope of HA, previous descriptions are limited, and it is possible to find information associated, above all, with atrial fibrillation (AF). Therefore, it is possible to mention that Hu et al. showed AF as the underlying disease in 2.4% of OPs.¹⁴ Although it is unfeasible to generalize the rate in question, a comparative view can be established, considering that AF constitutes the most common HA in the general population.¹⁵ Thus, it is noted that the number achieved does not differ substantially from the literature.

Table 1 – Sociodemographic, behavioral, and epidemiological characteristics related to the incidence of cardiovascular diseases (n=250)

Variables	Patients with incident cardiovascular diseases (n=34)		Patients without incident cardiovascular diseases (n=216)		p
	n	%	n	%	
Male sex	27	19.4	112	80.6	0.003*†
Age ≥ 60 years	21	15.6	114	84.4	0.328*
Smoking	16	21.1	60	78.9	0.023*†
Cardiovascular comorbidities	18	15.1	101	84.9	0.502*
Metabolic comorbidities	13	22.4	45	77.6	0.025*†
Pulmonary comorbidities	4	36.4	7	63.6	0.047††
Previous exposure to oncological therapy	2	9.1	20	90.9	0.748†
Current exposure to oncological therapy	34	14.3	203	85.7	0.225†

*Pearson's Chi-Square Test. †Fisher's Exact Test. ††Variable with statistical significance ($p < 0.05$).

Table 2 – Oncological therapies related to the incidence of cardiovascular diseases (n=250)

Variables	Patients with incident cardiovascular diseases after starting oncological therapy (n=33)		Patients without incident cardiovascular diseases after starting oncological therapy (n=217)		p
	n	%	n	%	
Surgery	18	11.2	143	88.8	0.204*
Radiotherapy	18	20.2	71	79.8	0.015*†
Chemotherapy	21	19.4	87	80.6	0.011*†
Hormone therapy	5	10.2	44	89.8	0.526*
Target therapy	6	27.3	16	72.7	0.052†

*Pearson's Chi-Square Test. †Fisher's Exact Test. ††Variable with statistical significance ($p < 0.05$).

Table 3 – Exclusively chemotherapy drugs related to the incidence of cardiovascular diseases (n=250)

Variables	Patients with incident cardiovascular diseases after starting oncological therapy (n=33)		Patients without incident cardiovascular diseases after starting oncological therapy (n=217)		p*
	n	%	n	%	
Capecitabine	2	20.0	8	80.0	0.626
Carboplatin	1	6.2	15	93.8	0.703
Cyclophosphamide	4	18.2	18	81.8	0.506
Cisplatin	6	19.4	25	80.6	0.266
Dacarbazine	1	33.3	2	66.7	0.347
Docetaxel	3	15.0	17	85.0	0.734
Doxorubicin	4	18.2	18	81.8	0.506
Etoposide	1	50.0	1	50.0	0.247
Fluorouracil	9	26.5	25	73.5	0.025†
Gemcitabine	2	12.5	14	87.5	1,000
Irinotecan	3	30.0	7	70.0	0.131
Oxaliplatin	6	30.0	14	70.0	0.033†
Paclitaxel	2	9.1	20	90.9	0.748
Vinblastine	1	50.0	1	50.0	0.247
Vincristine	3	42.9	4	57.1	0.051

*Fisher's Exact Test. †Variable with statistical significance ($p < 0.05$).

With regard to IHD, CHF, and PAD, it is worth recapitulating the studies by Youn et al. and Battisti et al., who respectively addressed specific prevalences 7.4%, 1.9% and 1.5% and 10.2%, 3.4% and 3.3%.^{10,11} In this circumstance, it appears that only IHD was not included in the range defined by the studies mentioned above, distancing itself by 3.8% from the lower limit. This may be linked to both the characteristics of the population and the methodology of the work being explained.

Additionally, a total incidence of CVDs of 13.6% in OPs was noted, which proved to be compatible with the literature. As an example, Youn et al. reported that 15.7% of OPs acquired CVD after CA, while Keegan et al. showed this occurrence in only 2.8% of OPs.^{10,16} However, it is worth noting that such research differs in terms of age group (20-85 years vs. 15-39 years), which justifies this percentage variation. In this context, it should be noted that the present study included all age groups, which supports the approximation to the rate of the broader work.

In the evaluation being elucidated, the predominance of DVT was highlighted, which presented a specific incidence of 4.4%. This disorder was followed by PE, SAH, AMI, and CHF, which sequentially included rates of 2.0%, 1.6%, 1.2% and 1.2%.

Regarding DVT and PE, it is noteworthy that there is a joint description in the literature, referred to as venous thromboembolism (VTE). This condition is frequently reported in cardio-oncology, as CAs are an independent risk factor for VTE.¹⁷ As evidence of this, the study conducted by Sallah et al. confirmed the presence of VTE in 7.8% of OPs.¹⁸ From this perspective, it is observed that the result obtained in the present analysis is consistent with the emphasized production.

In relation to SAH, Fraeman et al. reported an incidence of 32.2% in OPs, considering a recent onset disorder of any nature. This rate decreased as severity increased, being evident in severe hypertension and hypertensive crisis, in due order, 12.4% and 2.8%.¹⁹ In view of this, it is noted that the value found in the current research is close to the most severe conditions, which implies the formulation of a hypothesis of underdiagnosis of mild and moderate conditions, which cannot be confirmed due to the limitations of secondary data analysis.

From the IAM perspective, it is worth highlighting the study conducted by Patlolla et al. which verified current and previous CAs, respectively, in 2.5% and 4.6% of patients hospitalized due to this CVD.²⁰ Therefore, it is noted that the incidence of AMI is higher in individuals with previous CA, which may justify the lower rate obtained in the current analysis, since it was carried out in a short period, making the evaluation of long-term manifestations unfeasible.

In the context of CHF, Youn et al. scored an incidence of 4.2% in OPs.¹⁰ In this way, the current research demonstrated a considerably lower result, which may be related to the criteria used to identify this disorder in medical records, considering that complications may have more of the main diagnosis, in particular, in patients who followed death.

Given the understanding of incident CVDs, we sought to investigate the factors associated with the incidence of CVDs in OPs, which allowed the identification of significant differences in relation to male sex ($p = 0.003$), smoking ($p = 0.023$) and metabolic ($p = 0.025$) and pulmonary ($p = 0.047$) comorbidities.

In relation to the male sex, Keegan et al. also reported a propensity for CVDs in OPs; however, as reported in a previous section, this analysis was limited to adolescents and young adults.¹⁶ Thus, the current research expanded the perspective of comparison by including all age groups. In these circumstances, it should be noted that the elucidated result may be linked to the tendency for men to exhibit a greater number of FRCs.²¹ Furthermore, there is the possibility of this phenomenon occurring due to specific CAs, such as prostate CA, in which androgen deprivation therapy is used, which, in turn, predisposes the appearance of CVDs.²²

In reference to smoking, there is a strong association with CVD in the literature. This is related both to the substances in tobacco, such as nicotine, which activates the sympathetic nervous system, and to the by-products of cigarette combustion, such as oxidizing particles that result in inflammation, platelet activation, and endothelial dysfunction.²³ From this perspective, the factor in question provides a favorable scenario for CVDs, which is accentuated by the implications of CA. This reality was confirmed by Kenfield et al., who analyzed patients with prostate CA and described that smokers had a higher risk of mortality from CVDs.²⁴

Regarding metabolic and pulmonary comorbidities, it is highlighted that scientific studies indicate a panorama of shared repercussions, such as low-grade inflammation, oxidative stress, and endothelial dysfunction, which contribute incisively to the development of CVDs.²⁵⁻²⁷ From this perspective, it is relevant to highlight, for example, the research conducted by Oh et al., in which it was observed that survivors of CA with diabetes showed a higher risk of incident CVD, which reinforces the findings of the analysis being elucidated.²⁸

When evaluating current exposure to OT, no significant association was observed in relation to the incidence of CVDs ($p=0.225$). Therefore, a new analysis was carried out segmenting the therapeutic modalities, which made it possible to confer statistical significance concerning RT ($p=0.015$) and CT ($p=0.011$). These results are corroborated by cardio-oncological productions, such as the research conducted by Mulrooney et al., which revealed that exposure to cardiac radiation and anthracyclines substantially increased the relative risk of CVD in CA survivors.²⁹

In the scenario in question, it appears that OTs favor CVDs, mainly due to cardiotoxicity, that is, the ability to promote harmful effects on the cardiovascular system.³⁰ Therefore, it is possible to notice disorders in the blood vessels and heart that eventually progress to ventricular dysfunction and heart failure.³¹ In this logic, ADs are addressed more frequently, due to the variety of clinical repercussions, not limited to anthracyclines.³²

Given the understanding of cardiotoxicity, an attempt was made to evaluate the ADs administered to OPs with incident CVDs. For this purpose the investigation of ECDs was emphasized, as the results were significant for CT. Therefore, statistical relevance was observed for fluorouracil ($p=0.025$) and oxaliplatin ($p=0.033$).

Fluorouracil is an antimetabolite that exerts cytotoxic action on CAs, mainly through the inhibition of thymidylate synthase, which acts in the formation of thymidine, which, in turn, is vital in the synthesis of deoxyribonucleic acid (DNA).³³ However, there is a direct relationship with CVDs, which was highlighted, as an

example, in the study conducted by Peng et al., which revealed the presence of cardiotoxic manifestations, such as IHD and HA, in 25.0% of OPs that used the substance in explanation.³⁴

On the other hand, oxaliplatin is an alkylating agent whose activity is mainly associated with the formation of cross-links in polynucleotide chains, which results in the interruption of DNA replication and, therefore, the destruction of CAs.³⁵ In the context of platinum-based drugs, oxaliplatin is predominantly linked to neurotoxicity and less frequently associated with cardiovascular toxicity.³⁶ However, it is noteworthy that this substance is commonly combined with fluorouracil and folinic acid, particularly in patients with colorectal CA, which may have led to an equivocal result in the analysis in evidence.³⁷

It should also be noted that anthracyclines, represented essentially by doxorubicin, did not show substantial differences in the current research ($p=0.506$). This may be related to the fact that the investigation of the cardiotoxicity of these ADs supported the development of cardio-oncology.⁹ In this way, such cardiotoxic mechanisms were understood early, which allowed the formulation and dissemination of preventive strategies, which provided a lower cardiovascular impact, as evidenced in the results mentioned above.

Based on the information recorded, the complexity of preventing, detecting, and managing CVDs in OPs becomes apparent, since there is a multifactorial etiology that encompasses individual characteristics and therapeutic particularities. In this context, the implementation of cardiovascular monitoring is vital, especially after submission to OTs, since the identification of CVDs in reversible phases can favor the prognosis of OPs.

Finally, it is important to highlight that the research in evidence was conducted based on medical records and, therefore, is exposed to the limitations inherent to the secondary data approach. Therefore, it is worth emphasizing the possibility of selection and information biases, as such documents may contain incomplete records and, in addition, incorporate the subjective interpretation of the employees responsible for filling them out. Despite this, the data were evaluated in detail, aiming to follow all the criteria stipulated in the methodological design strictly.

Conclusions

In general, the study revealed a significant relationship between CAs and CVDs, highlighting a higher incidence associated, after a CA diagnosis, with male sex, smoking, and metabolic and pulmonary comorbidities and, after submission to OT, linked to RT, and CT, in particular, fluorouracil and oxaliplatin. In this way, the relevance of intensifying synergy between cardiologists and oncologists from the perspective of combating CA became clear, especially taking into account the possibility of mitigating the harmful effects on the cardiovascular system.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for

important intellectual content: Lorencini GA, Rabello RS; Acquisition of data: Lorencini GA.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal da Fronteira Sul under the protocol number 5.180.104. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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