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ORIGINAL ARTICLE

Impact of a cardio-oncology unit on prevention of cardiovascular events in cancer patients

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Abstract

Aims As the world population grows older, the co-existence of cancer and cardiovascular comorbidities becomes more common, complicating management of these patients. Here, we describe the impact of a large Cardio-Oncology unit in Southern Italy, characterizing different types of patients and discussing challenges in therapeutic management of cardiovascular complications.

Methods and results We enrolled 231 consecutive patients referred to our Cardio-Oncology unit from January 2015 to February 2020. Three different types were identified, according to their chemotherapeutic statuses at first visit. Type 1 included patients naïve for oncological treatments, Type 2 patients already being treated with oncological treatments, and Type 3 patients who had already completed cancer treatments. Type 2 patients presented the highest incidence of cardiovascular events (46.2% vs. 12.3% in Type 1 and 17.9% in Type 3) and withdrawals from oncological treatments (5.1% vs. none in Type 1) during the observation period. Type 2 patients presented significantly worse 48 month-survival (32.1% vs. 16.7% in Type 1 and 17.9% in Type 3), and this was more evident when in the three groups we focused on patients with uncontrolled cardiovascular risk factors or overt cardiovascular disease at the first cardiologic assessment. Nevertheless, these patients showed the greatest benefit from our cardiovascular assessments, as witnessed by a small, but significant improvement in ejection fraction during follow-up (Type 2b: from 50 [20; 67] to 55 [35; 65]; $P = 0.04$).

Conclusions Patients who start oncological protocols without an accurate baseline cardiovascular evaluation are at major risk of developing cardiac complications due to antineoplastic treatments.

Keywords Cardio-oncology; Cardiotoxicity; Cardiovascular risk factors; Heart failure; Cancer

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Introduction

Understanding the complex link between cardiovascular diseases (CVDs) and cancer has become pivotal for Cardio-Oncology, considering that together these two diseases are the main causes of death in industrialized countries.[1–4] As the world population grows older, the incidence of cancer and heart diseases rises, either as separate diseases or as concomitant conditions.[5–7] However, thanks to constant improvements in anticancer treatments, including new drugs

and new protocols, cancer patients' survival has tremendously increased over the past decade.[8]

It is well known that many antineoplastic drugs may induce different types of cardiotoxicities, such as arterial hypertension, thrombotic events, arrhythmias, and heart failure (HF) and that the development of cardiotoxicity is still a burden to the completion of some chemotherapeutic protocols.[9] Nevertheless, it is clear that the relationship between cancer and CVDs is not only limited to cardiotoxicity[10] but also involves shared risk factors, such as smoking, obesity, and ageing.[1,3,4,11–14]

The growing awareness of the tight link between CVDs and cancer has led to the formation of multidisciplinary teams in which different experts, including cardiologists, oncologists, haematologists, radiologists, and surgeons, cooperate to guarantee the best possible care tailored to each patient.[15,16] Consequently, Cardio-Oncology has become critical for the correct management of cancer patients, with growing interest in tools not only able to predict early cardiotoxicity but also able to assess the risk of each patient to develop cardiac damage associated with antineoplastic treatments.[17,18]

In the present manuscript, we describe the activity of our Cardio-Oncology Unit, characterize the different types of patients referred to our unit, and discuss the challenges in therapeutic management of cardiovascular (CV) complications.

Methods

Study design

This is a single-centre prospective study based in our Cardio-Oncology Unit in the Department of Translational Medical Sciences, Federico II University, Naples, Italy. The protocol was approved by the local ethics committee, the study was conducted following the Helsinki Declaration principles, and all patients signed a written informed consent to participate to the study. The vast majority of patients included in the study were consecutive cases who were referred to our Unit from major Oncology University Clinics such as the Haematology and the Oncology Divisions of the Department of Clinical Medicine and Surgery of the Federico II University of Naples, and the Division of Oncology, Department of Precision Medicine, Luigi Vanvitelli University of Campania, Naples, Italy. A few patients were referred from smaller oncology units in the Naples area.

Inclusion criteria were age $>$ 18 years; patients newly diagnosed with cancer with indication to oncological treatments, or patients already on anticancer treatment, or patients who had been previously administered with anticancer treatments; and availability of at least two visits in our cardio-oncology unit, at least 1 month apart from one another.

Cardio-oncology evaluation

According to current recommendations,[9,19–21] cardio-oncology evaluations consisted of full patients history, including lifestyle (diet, activity, and smoking habits), family history of cardiac disease, any coexistent illnesses and ongoing therapies, and previous diseases and therapies; complete physical examination, blood pressure measurement, and resting 12-lead electrocardiogram; and 2D echocardiography[22] and blood tests, including biomarkers such as N-terminal pro-brain natriuretic peptide and cardiac Troponin I.[21,23]

Standard transthoracic 2D-echocardiographic examinations were performed using a Philips iE33 ultrasound machine (Phillips Healthcare, Andover, MA). Images were obtained using a 3.4 MHz transducer, and patients were in left lateral decubitus position. Following the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines, standard subxiphoid, apical, and parasternal windows were visualized to acquire 2D images of the cardiac chambers, colour, pulsed-wave, and continuous-wave Doppler measurements, in order to asses systolic and diastolic heart function.[24]

To evaluate cardiac function, we analysed left ventricular (LV) ejection fraction (EF), obtained from the apical four-chamber and two-chamber views using the modified Simpson's rule.[25,26]

Clinical phenotyping of the study population

Patients were classified in three different clinical types, according to their oncological statuses at the first clinical visit, as follows:

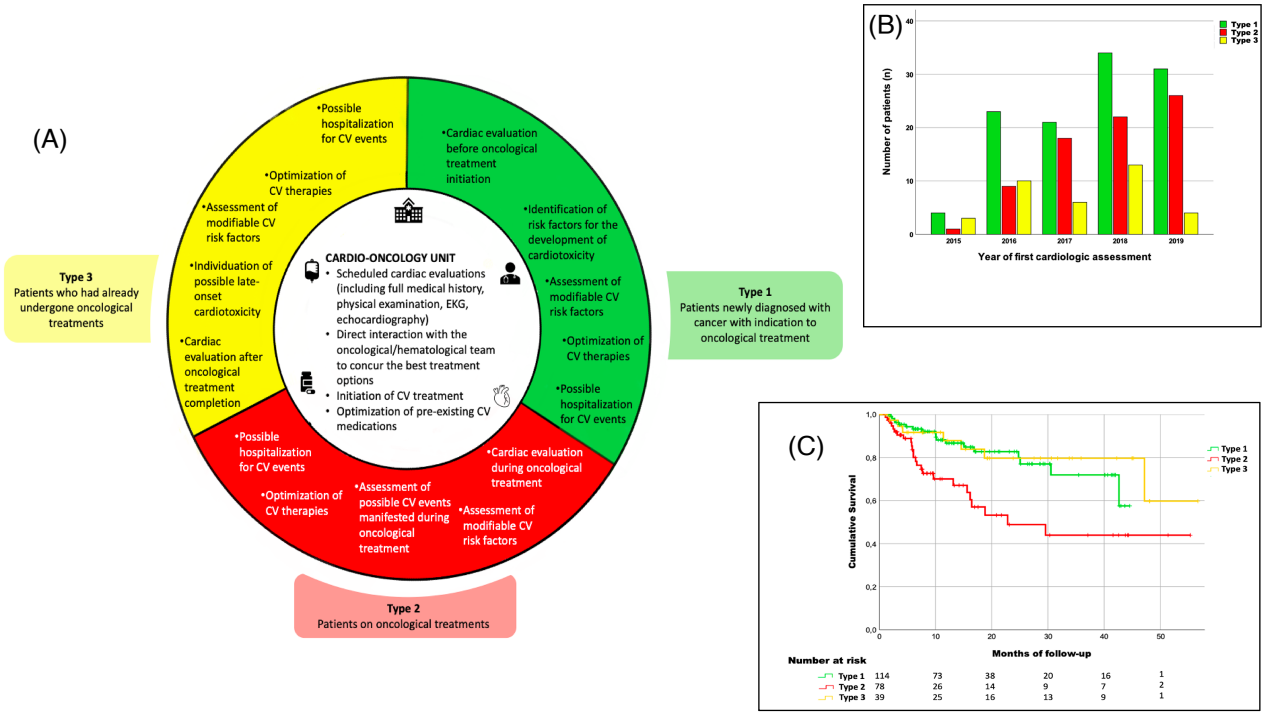
- Type 1: Patients newly diagnosed with cancer, naïve for oncologic treatments.
- Type 2: Patients on oncological treatments.
- Type 3: Patients who had already completed oncologic treatments.

Figure 1A summarizes this classification.

Follow-up visits

Patients underwent cardiological evaluations every 3 or 6 months or more often, according to their type or their clinical needs. In particular, patients were evaluated every 3 months until 1 year after the completion of anticancer treatments, then every 6 months for 5 years, and then once a year, or when clinically needed.

Figure 1 (A) Graphic picture of the different types of patients referring to our Cardio-Oncology Unit and of the most relevant challenges to be addressed by cardio-oncology specialists. (B) Bar graph of the distribution baseline assessment from 2015 to 2020, according to the three patient types. (C) Kaplan–Meier curves according to the three patient types. CV, cardiovascular.



Outcomes

Outcome occurrence was defined by the presence of one of the following clinical scenarios: (i) all CV events (including hospitalization) during follow-up; (ii) CV events requiring oncologic therapeutic protocol modification or temporary suspension; (iii) CV events requiring definitive oncologic therapeutic protocol withdrawal; and (iv) death for all causes.

Moreover, data on CV treatment optimization (defined as modification of CV therapies already prescribed to the patient) or on *de novo* CV treatment initiation were also collected.

The presence of CV events was defined according to the 2016 European Society of Cardiology Consensus paper on cardiotoxicity by Zamorano et al.[9] and the expert opinion of our team of cardio-immuno-oncology specialists. The decision to modify, temporary suspend, or withdraw antineoplastic treatment was discussed with the referring oncologist for each patient, taking into account risks and benefits.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normal distribution of continuous variables. Data are presented as mean ± standard deviation for normally distributed continuous variables, as median [minimum; maximum] for not normally distributed continuous variables, and as absolute numbers or percentage for discrete variables. Fisher's exact test was used to compare discrete variables among types. Continuous variables were analysed using one-way ANOVA when normally distributed or the one-way ANOVA on ranks test when not normally distributed to explore differences among types. Differences in echo-derived LVEF from baseline to the last follow-up visit were assessed using the Wilcoxon test.

A P-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics Version 24 (IBM, Armonk, New York).

Results

Cardiovascular characteristics of the whole population at the first cardiologic assessment according to three types

From January 2015 to February 2020, a total of 374 subjects were referred to our outpatient Cardio-Oncology Unit. Among them, 231 patients (mean age 60.8 ± 15.4; 50.2% females) met the inclusion criteria and were enrolled in the study. *Figure 1B* schematizes the distribution of baseline as-

sessment from 2015 to 2020, according to three types. Baseline general characteristics are described in *Table 1*. Median follow-up period was 11 [1.0; 56.7] months.

Naïve patients, identified as Type 1, represent the majority of our study population.

As shown in *Table 1*, there were no significant differences between the three types, except for gender distribution and length of follow-up in months. In particular, Type 1 presented the lowest prevalence of female patients (40.4%) compared with Type 2 (60.3%) and Type 3 (59.0%) ($P = 0.012$). Median follow-up in Type 1 was 13.3 [1.1; 54.7] months, in Type 2 was 7.6 [1.0; 55.3], and in Type 3 was 18.7 [1.1; 56.7] ($P < 0.01$).

Cancer characteristics and protocols according to three types

Data on cancer characteristics, including cancer stage and antineoplastic protocols, are presented in *Table 1*. In particular, 65 (28.2%) patients had colon cancer, 53 (22.9%) patients had lymphomas, 30 (13.0%) patients were affected by breast cancer, 19 (8.2%) patients were diagnosed with skin melanoma, 15 (6.5%) patients were diagnosed with gastric cancer, 9 (3.9%) patients had lung cancer,7 (3.0%) patients were diagnosed with other gastrointestinal cancers than gastric and colon cancers, 5 (2.2%) patients presented prostate cancer, 4 (1.7%) patients were affected by feminine genital neoplasms, and 24 (10.4%) patients had cancer in other sites not mentioned above, such as oropharyngeal, thyme, and kidneys.

Median latency from last oncological treatment and first cardiologic evaluation was 64.0 [1.8; 1374.7] months for Type 3 patients.

Data on cancer stage were available for 165 patients. Of these, 7.9% had Stage 1 cancer; 12.7% of patients presented Stage 2 neoplasms; 26.1% presented Stage 3; and the majority of patients, 53.3%, had Stage 4 tumours. Data on cancer surgery and radiotherapy were available for 225 patients. In particular, 140 patients (62.5%) had surgery and 87 patients (38.7%) were also administered with radiation therapy.

Additional data on cancer characteristics and stage, surgery, and radiation therapy for each type of patients are shown in *Table 1*.

Concerning antineoplastic treatments, 22.5% of the general population was treated with antineoplastic protocols based on vascular endothelial growth factor (VEGF) inhibitors and/or endothelial growth factor receptor inhibitors possibly associated with other agents (i.e. taxanes, platinum-derived compounds, pyrimidine analogues, gemcitabine, irinotecan, and etoposide). As for anti-VEGF drugs, 76% of our patients were treated with bevacizumab, while the remaining percentage is treated with other anti-VEGF agents. Fifty-three patients (22.9%) were treated with protocols based on pyrimidine analogues and/or platinum-derived compounds, possibly associated with other antineoplastic agents (i.e. taxanes, gemcitabine, irinotecan, and etoposide). Sixty-four patients (27.7%) were treated with anthracyclines-based chemotherapeutic protocol. On the other hand, 15 lymphoma patients were treated with non-anthracyclines-based chemotherapy and were administered, for instance, with rituximab associated to bendamustin, mitoxantrone, and fludarabine. Eleven patients were treated with MEK and BRAF inhibitors. Six patients were treated with immunotherapy. Ten patients (4.3%) were treated with hormone-based therapies. Finally, 20 patients (8.7%) were treated with antineoplastic protocols other than those mentioned above. *Table 1* shows data on cancer therapies according to each patient type.

Follow-up

During follow-up, 25 patients (10.8%) were newly diagnosed with systemic hypertension, 4 patients (1.7%) were diagnosed with HF with reduced ejection fraction, and 11 patients (4.8%) developed new-onset atrial fibrillation. Furthermore, one Type 2 patient experienced acute myocardial infarction during follow-up. Hence, several patients needed optimization of their pre-existing CV treatments. In particular, in 33 patients (14.3%), we up-titrated beta-blockers dosages. In 12 patients (5.2%), the dosage of angiotensin-converting enzyme inhibitor was increased. In 11 patients, the dose of angiotensin receptor blockers was up-titrated. One patient (0.4%) belonging to Type 3 was up-titrated with mineralocorticoid receptor antagonists. In four patients (1.7%), the dosage of antiplatelet therapy was increased. In 11 patients (4.8%), statin dose was increased, while in 8 patients (3.5%), the dose of diuretics was up-titrated. In five patients (2.2%), there was an up-titration of calcium channel blockers. Finally, one patient (0.4%) belonging to Type 2 was prescribed with higher doses of angiotensin receptor neprilysin inhibitor (ARNI) during follow-up.

In addition, 55 patients (23.8%) needed to start beta-blockers. Twenty-two patients (9.5%) started angiotensin-converting enzyme inhibitors. In seven patients (3.0%), angiotensin receptor blockers were newly prescribed. Moreover, 11 patients (4.8%) were initiated with mineralocorticoid receptor antagonists, 59 patients (25.5%) were administered with antiplatelet therapy, and 58 patients (25.1%) were prescribed with statins. Furthermore, 33 patients (14.3%) started diuretics, and 14 patients (6.1%) calcium channel blockers. Finally, 17 patients (7.4%) needed anticoagulation treatment, while 3 patients (1.3%) were started with ARNI.

Table 2 summarizes the modifications of CV treatments in the study population during follow-up and the main reasons to introduce new CV treatment.

Table 1 General characteristics of the study population at the first cardiologic assessment, including cancer types, cancer stages, and antineoplastic treatments

Variables	All (n = 231)	Type 1 (n = 114)	Type 2 (n = 78)	Type 3 (n = 39)	P-value
Age	60.8 ± 15.37	66.7 ± 15.7	60.2 ± 14.7	62.4 ± 16.0	0.0764
Female, n (%)	116 (50.2)	46 (40.4)	47 (60.3)	23 (59.0)	**0.012**
Months of follow-up	11.0 [1.0; 56.7]	13.1 [1.1; 44.5]	7.6 [1.0; 55.3]	18.7 [1.1; 56.7]	<**0.01**
Number of echocardiography, n	3 [2.0; 18.0]	4 [2.0; 18.0]	3 [2.0; 18.0]	3 [2.0; 9.0]	0.999
SBP at first cardiologic assessment	130 [90; 180]	130 [90; 180]	130 [100; 180]	130 [90; 170]	0.362
DBP at first cardiologic assessment	80 [60; 120]	80 [60; 110]	80 [60; 120]	80 [60; 100]	0.187
HR at first cardiologic assessment	80 [39; 114]	70 [39; 107]	70 [52; 114]	65 [54; 110]	0.239
LVEF at first cardiologic assessment	55 [20; 67]	56 [33; 65]	55 [20; 67]	55 [33; 65]	0.203
Concomitant conditions, n (%)					
Diabetes mellitus	40 (17.3)	22 (19.2)	12 (15.4)	6 (15.4)	0.734
Hypertension	141 (60.0)	66 (57.9)	52 (66.7)	23 (59.0)	0.453
Active smoking	52 (22.5)	26 (22.8)	21 (26.9)	5 (12.8)	0.226
Previous smoking	59 (25.5)	37 (32.5)	15 (19.2)	7 (17.9)	0.058
Dysthyroidism	27 (11.7)	10 (8.8)	11 (14.1)	6 (15.4)	0.388
Dyslipidaemia	81 (35.1)	42 (36.8)	27 (34.6)	12 (30.8)	0.786
Carotid atherosclerosis	37 (16.1)	23 (20.2)	9 (11.5)	5 (12.8)	0.232
BMI 25–29.9 overweight	93 (40.3)	46 (40.4)	30 (38.5)	17 (43.6)	0.867
BMI ≥ 30 obese	31 (13.4)	14 (12.2)	12 (15.4)	5 (12.8)	0.819
COPD	18 (7.8)	13 (11.4)	3 (3.8)	2 (5.1)	0.199
Atrial fibrillation	26 (11.3)	12 (10.5)	11 (14.1)	3 (7.7)	0.552
LV dysfunction	36 (15.6)	13 (11.4)	16 (20.5)	7 (17.9)	0.210
Previous MI	27 (11.7)	19 (16.7)	6 (7.7)	2 (5.1)	0.062
PM implant	7 (3.0)	4 (3.5)	2 (2.6)	1 (2.6)	0.916
Valvular heart disease	9 (3.9)	5 (4.4)	2 (2.6)	2 (5.1)	0.741
HCM	1 (0.43)	0 (0)	1 (1.3)	0 (0)	0.373
Concentric LV remodelling	48 (20.8)	22 (19.3)	19 (24.4)	7 (17.9)	0.622
Other CVDs	20 (8.7)	6 (5.3)	11 (14.1)	3 (7.7)	0.099
CV treatments at first visit, n (%)					
Beta-blockers	93 (40.2)	43 (37.7)	33 (42.3)	17 (43.6)	0.733
ACEi	63 (27.3)	28 (24.6)	28 (35.9)	7 (17.9)	0.080
ARBs	46 (19.9)	23 (20.2)	14 (17.9)	9 (23.1)	0.803
MRAs	11 (4.8)	4 (3.5)	5 (6.4)	2 (5.1)	0.646
APT	61 (26.4)	29 (25.4)	20 (25.6)	12 (30.8)	0.821
Statin	57 (24.7)	34 (29.8)	17 (21.8)	6 (15.4)	0.122
Diuretics	56 (24.2)	24 (21.1)	19 (24.4)	13 (33.3)	0.303
CCBs	35 (15.5)	18 (15.8)	13 (16.7)	4 (10.3)	0.637
ARNI	2 (0.9)	1 (0.9)	1 (1.3)	0 (0)	0.779
Cancer type, n (%)					
Gastric	15 (6.5)	7 (6.1)	5 (6.4)	3 (7.7)	0.943
Colon	65 (28.2)	34 (29.8)	26 (33.3)	5 (12.8)	0.057
Other sites in the GI apparatus	7 (3.0)	1 (0.9)	5 (6.4)	1 (2.6)	0.088
Lymphomas	53 (22.9)	32 (28.1)	7 (9.0)	14 (35.9)	<**0.01**
Breast	30 (13.0)	8 (7.0)	13 (16.7)	9 (23.1)	**0.036**
Melanoma	19 (8.2)	16 (14.0)	3 (3.8)	0 (0)	<**0.01**
Lungs	9 (3.9)	3 (2.6)	4 (5.1)	2 (5.1)	0.618
Feminine genital	4 (1.7)	1 (0.9)	3 (3.8)	0 (0)	0.199
Prostate	5 (2.2)	2 (1.8)	2 (2.6)	1 (2.6)	0.914
Other sites	24 (10.4)	10 (9.0)	10 (12.8)	4 (10.3)	0.665
Cancer stage, n (%)					
1	13 (7.9) [165]	6 (6.6) [91]	4 (6.6) [61]	3 (23.1) [13]	0.106
2	21 (12.7) [165]	14 (15.4) [91]	6 (9.8) [61]	1 (7.7) [13]	0.513
3	43 (26.1) [165]	31 (34.1) [91]	10 (16.4) [61]	2 (15.4) [13]	**0.034**
4	88 (53.3) [165]	40 (44.0) [91]	41 (67.2) [61]	7 (53.8) [13]	**0.019**
Metastatic	82 (37.1) [221]	39 (36.1) [108]	37 (48.7) [76]	6 (16.2) [37]	**0.003**
Cancer surgery, n (%)	140 (62.5) [225]	66 (59.5) [111]	52 (67.5) [77]	22 (59.5) [37]	0.496
Radiotherapy, n (%)	87 (38.7) [226]	37 (32.5)	34 (43.6)	16 (47.1) [34]	0.160
Latency from last oncological treatment to baseline assessment, months	NA	NA	NA	64 [1.8; 1374.7]	NA

(*Continues*)

Table 1 (continued)

Variables	All (n = 231)	Type 1 (n = 114)	Type 2 (n = 78)	Type 3 (n = 39)	P-value
Anticancer drugs, n (%)					
VEGF-based and/or EGFR-based protocols (± PA ± PDC ± other chemotherapeutic agents)	52 (22.5)	20 (17.5)	30 (38.5)	2 (5.1)	<**0.001**
PA-based and/or PDC-based protocols (± other chemotherapeutic agents)	53 (22.9)	31 (27.2)	17 (21.8)	5 (12.8)	0.175
Anthracyclines-based protocols	64 (27.7)	31 (27.2)	21 (26.9)	12 (30.8)	0.895
Non-anthracyclines-based schemes for lymphoma	15 (6.5)	8 (7.0)	1 (1.3)	6 (15.4)	**0.040**
MEKi ± BRAFi	11 (4.8)	9 (7.9)	2 (2.6)	0 (0)	0.073
Immunotherapy	6 (2.6)	6 (5.3)	0 (0)	0 (0)	**0.042**
Hormone-based protocols	10 (4.3)	1 (0.9)	2 (2.6)	7 (17.9)	<**0.001**
Others	20 (8.7)	8 (7.0)	5 (6.4)	7 (17.9)	0.076

ACEi, angiotensin-converting enzyme inhibitor; APT, antiplatelet therapy; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; BMI, body mass index; BRAFi, B-Raf inhibitors; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HCM, hypertrophic cardiomyopathy; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MEKi, mitogen-activated protein kinase kinase inhibitors; MI, myocardial infarction; MRAs, mineralocorticoid receptor antagonists; NA, not applicable; PA, pyrimidine analogues; PDC, platinum-derived compound; PM, pacemaker; SBP, systolic blood pressure; VEGF, vascular endothelial growth factor.
Data are expressed as median [minimum; maximum] for not normally distributed continuous variables, mean ± standard deviation for normally distributed continuous variables, and number and percentage for discrete variables. Bold P-values identify statistically significant values.

Table 2 Modifications of cardiovascular treatments in the study population during follow-up

	All (n = 231)	Type 1 (n = 114)	Type 2 (n = 78)	Type 3 (n = 39)	P-value
CV treatment optimization, n (%)					
Beta-blockers	33 (14.3)	13 (11.4)	14 (17.9)	6 (15.4)	0.435
ACEi	12 (5.2)	6 (5.3)	4 (5.1)	2 (5.1)	0.999
ARBs	11 (5.2)	3 (2.6)	4 (5.1)	4 (10.3)	0.153
MRAs	1 (0.4)	0 (0)	0 (0)	1 (2.6)	0.084
APT	4 (1.7)	2 (1.8)	2 (2.6)	0 (0)	0.605
Statin	11 (4.8)	7 (6.1)	4 (5.1)	0 (0)	0.294
Diuretics	8 (3.5)	4 (3.5)	2 (2.6)	2 (5.1)	0.774
CCBs	5 (2.2)	4 (3.5)	1 (1.3)	0 (0)	0.346
ARNI	1 (0.4)	0 (0)	1 (1.3)	0 (0)	0.373
CV treatment initiation, n (%)					
Beta-blockers	55 (23.8)	25 (21.9)	22 (28.2)	8 (20.5)	0.526
ACEi	22 (9.5)	11 (9.6)	5 (6.4)	6 (15.4)	0.296
ARBs	7 (3.0)	3 (2.6)	4 (5.1)	0 (0)	0.294
MRAs	11 (4.8)	5 (4.4)	5 (6.4)	1 (2.6)	0.632
Amiodarone	8 (3.5)	2 (1.8)	6 (7.7)	0 (0)	**0.037**
APT	59 (25.5)	28 (24.6)	25 (32.1)	6 (15.4)	0.141
Statin	58 (25.1)	25 (21.9)	21 (26.9)	12 (30.8)	0.493
Diuretics	33 (14.3)	12 (10.5)	11 (14.1)	10 (25.6)	0.066
CCBs	14 (6.1)	7 (6.1)	4 (5.1)	3 (7.7)	0.860
Anticoagulation	17 (7.4)	8 (7.0)	7 (9.0)	2 (5.1)	0.740
ARNI	3 (1.3)	1 (0.9)	2 (2.6)	0 (0)	0.439
Reason for cardiac medical intervention, n (%)					
LV systolic dysfunction	4 (1.7)	2 (1.8)	1 (1.3)	1 (2.6)	0.882
Systemic hypertension	25 (10.8)	11 (9.6)	9 (11.5)	5 (12.8)	0.833
Coronary artery disease	1 (0.4)	0 (0)	1 (1.3)	0 (0)	0.373
Arrhythmias	11 (4.8)	5 (4.4)	3 (3.8)	3 (7.7)	0.632
DVT/PE	8 (3.5)	3 (2.6)	3 (3.8)	2 (5.1)	0.743

ACEi, angiotensin-converting enzyme inhibitors; APT, antiplatelet therapy; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; CCBs, calcium channel blockers; CV, cardiovascular; DVT/PE, deep vein thrombosis/pulmonary embolism; LV, left ventricular; MRAs, mineralocorticoids receptor antagonists.
Data are expressed as number and percentage. Bold P-values identify statistically significant values.

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Outcomes

Left ventricular ejection fraction was evaluated almost at every visit. Data from the first and last available echocardiograms were compared. In particular, LVEF at the last visit did not differ significantly compared with the first visit in all three types, as shown in Supporting Information, *Figure S1A*. In particular, in Type 1, LVEF was 56% [33; 65] and 55% [37; 65] at the first and last echocardiographic assessment, respectively (P = 0.168). In Type 2, LVEF changed from 55% [20; 67] at the first echocardiographic assessment to 55% [35; 65] at the last echocardiographic assessment (P = 0.199). In Type 3, LVEF was 55% [33; 65] and 55% [25; 65] at the first and last echocardiographic assessment, respectively (P = 0.417).

We then explored CV events occurrence during follow-up. Outcomes data for the general population according to each patient type are shown in *Table 3*. Fifty-seven patients (24.7%) presented CV events during follow-up, with the highest prevalence in Type 2 patients (63.2% of all CV events registered during follow-up, corresponding to 46.2% of Type 2 patients). Among the 57 patients, 21 patients (18 from Type 2) presented CV events requiring oncologic therapeutic protocol modification or temporary suspension, while 4 patients, all belonging to Type 2, had to withdraw oncologic therapeutic protocols due to severe CV events. The most frequent CV events registered were new-onset atrial fibrillation, subclinical (increase in N-terminal pro-brain natriuretic peptide levels[23]) or clinical worsening of LV function (decrease of LVEF[22]) during oncologic therapy administration, new-onset dyspnoea, and deep vein thrombosis during chemotherapy administration.

Fifty-one patients (22.1%) died during follow-up due to other causes than CV: almost 50% (25 patients) belonged to Type 2. As shown in *Figure 1C*, Kaplan–Meier curves according to the three types suggest that Type 2 patients present worse 48 months of survival (log rank P = 0.001). As per *Table 4*, Cox regression performed for each group of patients did not show higher incidence of worse outcome with Stage IV cancer disease.

Considering that Type 2 patients also presented the highest incidence of CV events during follow-up, we then explored the role of pre-existing CVDs in this setting, and we further stratified each of the three types into two subgroups, as shown in *Figure 2*:

a Patients with no CV risk factors or well-controlled CV risk factors at the first cardiologic assessment.
b Patients with uncontrolled CV risk factors or overt CVD at the first cardiologic assessment.

General characteristics of the population, according to the six different types of patients, including data regarding cancer characteristics, stage, and treatment, are shown in Supporting Information, *Table S1*.

As shown in *Table 5*, the incidence of CV events during follow-up was 14.3% (4 out of 28 patients) for Type 2a and 64% (32 out of 50 patients) for Type 2b. Furthermore, 16 (32.0%) patients in Type 2b had to modify or temporarily suspend oncological treatments compared with 2 (7.1%) patients in Type 2a (Supporting Information, *Table S2*). As already stated, four patients, all belonging to Type 2b (8.0%), had to withdraw oncological treatments because of their CV comorbidities (overall P-value among six types = 0.012). Concerning mortality for all causes, 7 (25.0%) patients from Type 2a died during follow-up, compared with 18 (36.0%) from Type 2b.

The same trend was present in the other patient types. In particular, incidence of CV events during follow-up was 9.8% (6 out of 61 patients) in Type 1a vs. 15.1% (8/53) in Type

Table 3 Clinical outcomes according to three types

Clinical indication	All (n = 231)	Type 1 (n = 114)	Type 2 (n = 78)	Type 3 (n = 39)	P-value
CV events during follow-up, n (%)	57 (24.7)	14 (12.3)	36 (46.2)	7 (17.9)	**0.004**
Cancer treatment modification or temporary suspension, n (%)	21 (9.1)	3 (2.6)	18 (23.1)	NA	**<0.001**
Cancer treatment withdrawal, n (%)	4 (1.7)	0 (0)	4 (5.1)	NA	**0.015**
Death for all causes, n (%)	51 (22.1)	19 (16.7)	25 (32.1)	7 (17.9)	**0.03**

CV, cardiovascular; NA, not applicable.
Data are expressed as number and percentage. Bold P-values identify statistically significant values.

Table 4 Cox analysis for survival according to the three different types of patients

Variables	Type 1	P-value	Type 2	P-value	Type 3	P-value
Cancer Stage I	1.075 [0.138; 8.392]	0.945	1.308 [0.171; 10.022]	0.796	0.030 [0.00; 14 075.165]	0.598
Cancer Stage II	0.309 [0.039; 2.450]	0.266	0.036 [0.00; 12.602]	0.267	0.043 [0.00; 4.586E[11]]	0.837
Cancer Stage III	0.643 [0.171; 2.416]	0.514	1.385 [0.311; 6.178]	0.669	0.041 [0.00; 6 678 401.78]	0.740
Cancer Stage IV	2.508 [0.786; 8.004]	0.120	1.850 [0.530; 6.288]	0.340	52.813 [0.001; 5 169 491.92]	0.449

Figure 2 Graphical picture of the major findings. CV, cardiovascular; CVD, cardiovascular disease.

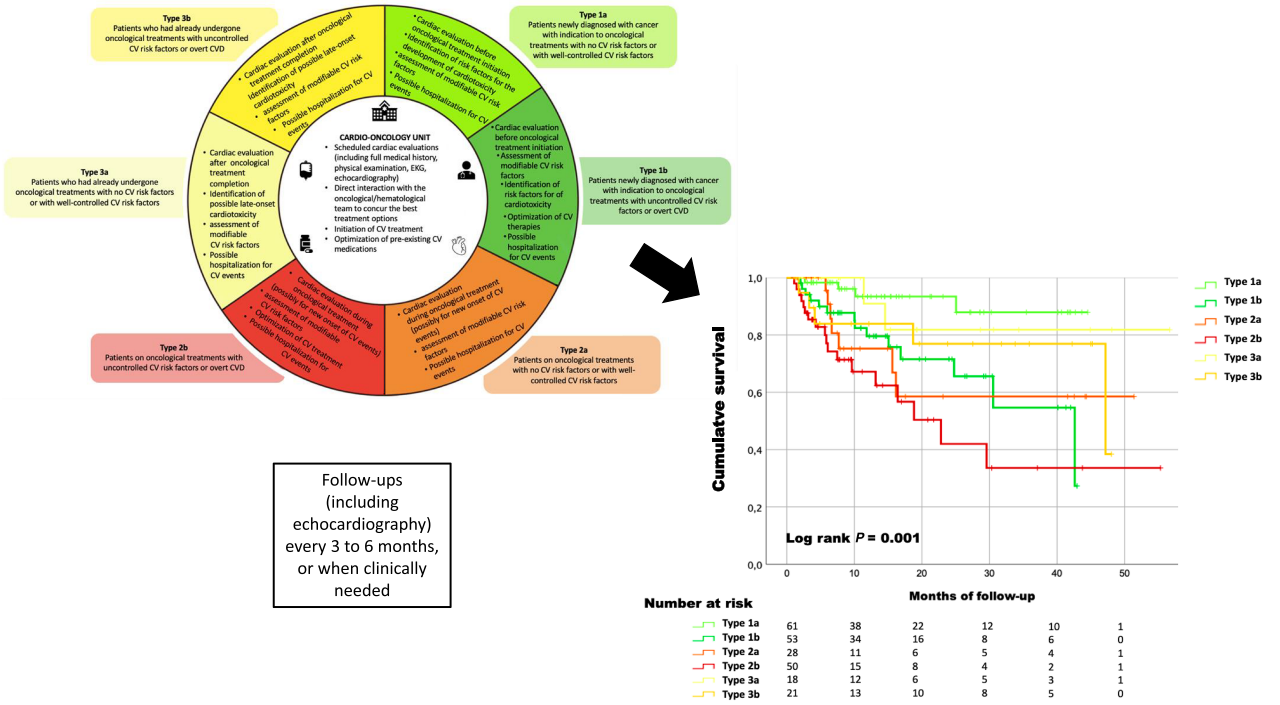

Table 5 Clinical outcomes among the six different types

Clinical indication	All (n = 231)	Type 1a (n = 61)	Type 1b (n = 53)	Type 2a (n = 28)	Type 2b (n = 50)	Type 3a (n = 18)	Type 3b (n = 21)	P-value
CV events during follow-up, n (%)	57 (24.7)	6 (9.8)	8 (15.1)	4 (14.3)	32 (64.0)	2 (11.1)	5 (23.8)	**0.012**
Cancer treatment modification or temporary suspension, n (%)	21 (9.1)	2 (3.3)	1 (1.9)	2 (7.1)	16 (32.0)	0 (0)	0 (0)	**<0.01**
Cancer treatment withdrawal, n (%)	4 (1.7)	0 (0)	0 (0)	0 (0)	4 (8.0)	0 (0)	0 (0)	**0.012**
Death for all causes, n (%)	51 (22.1)	4 (6.6)	15 (28.3)	7 (25.0)	18 (36.0)	2 (11.1)	5 (23.8)	**<0.01**

CV, cardiovascular.
Data are expressed as number and percentage. Bold P-values identify statistically significant values.

1b, and 11.1% (2/18) in Type 3a vs. 23.8% (5/21 patients) in Type 3b (overall P-value among six types = 0.012). Two patients out of 61 (3.3%) and one out of 53 (1.9%) patients from Type 1a and 1b, respectively, had to modify or temporarily suspend oncological treatments (overall P-value among six types < 0.01). During follow-up, 4 (6.6%) patients in Type 1a vs. 15 (28.3%) in Type 1b, and 2 (11.1%) patients in Type 3a vs. 5 (23.8%) patients in Type 3b died for all causes (overall P-value among six types < 0.01).

These data evidence a significantly worse survival of Type 2b patients compared with other subgroups (log rank $P < 0.001$ for Kaplan–Meier curves for 48 months of survival; *Figure 2*).

Nevertheless, comparing LVEF between the first and last echocardiogram available, patients belonging to Type 2b and Type 3a presented significant improvements in LV systolic function during follow-up. In particular, as shown in Supporting Information, *Figure S1B*, LVEF of Type 2b patients improved slightly but significantly (P = 0.04) between the first and last echocardiographic assessment. In Type 3a, LVEF also improved significantly (P = 0.02) between the first and last echocardiographic assessment.

Discussion

As the population grows older, the prevalence of both CVDs and cancer increases[1,4,7,11,27]; hence, a greater number of patients are being referred to cardio-oncology units.[15,16,28,29] In

this real-world study, we characterize the different types of patients who have been referred daily to our Cardio-Oncology Unit from two major Oncology University Clinics (Federico II University and Vanvitelli University, both in Naples, Italy) and from minor oncology facilities in the Naples area, and describe the different clinical challenges that we have been addressing when dealing with these patients. Our study highlights the importance of a continuous cardiologic follow-up in cancer patients, starting from a careful baseline CV assessment, as recommended by the recent position paper from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology,[21] hence tailoring follow-up to patients' specific characteristics.[22,23]

Our data show that patients who start oncologic protocols without an accurate baseline CV evaluation are at major risk of developing cardiac complications due to antineoplastic treatments. Indeed, the first step, when dealing with such complex patients as those affected by cancer and CV diseases, is addressing CV risk factors and optimizing CV treatment.[21] Importantly, optimization of CV therapies may require some time due to the need of up-titration of certain drugs (e.g. beta-blockers or ARNI). On the other hand, patients who were already being treated with oncologic therapies (Types 2a and 2b) may have been referred to cardiologic consultation already when presenting CV symptoms and, in this case, cardiologists need to ensure the best available medical options to each patient, trying to optimize CV therapy in order to let patients complete the most appropriate antineoplastic treatments, taking into account all comorbidities.[15,16,28]

Moreover, with long-term follow-up of patients who underwent previous oncologic treatments (Type 3), we aim at (i) managing patients who had already experienced CV events and (ii) surveilling patients who had not experienced CV events during or after oncologic treatments.

Considering the data from our 5 year follow-up, patients in Type 2a (and even more in Type 2b) present with the highest challenges according to their CV concomitant conditions. These patients face more CV events, either 'mild' (such as new-onset atrial fibrillation, or cardiac biomarkers elevation with no change in EF) or 'severe' (such as overt HF or myocardial infarction) needing for temporary suspension, modification, or even withdrawal of oncological treatment protocols. Our findings stress the concept that baseline cardiac evaluation is needed to ensure a correct assessment and management of each patient, reducing the risk of CV complications from oncologic therapies and also ameliorating the adhesion to oncological treatment protocols. Specifically, in our population, only four patients, who were referred to our Cardio-Oncology Unit for severe CV comorbidities when they were already on oncologic treatments (Type 2b), had to withdraw antineoplastic treatments.

Figure 2 summarizes the major findings of the manuscript.

Study limitations and conclusions

The major limitation to our study is the rather small sample size, considering that the patients are further divided into smaller groups, according to their cancer and CV status, resulting in even smaller subgroups. Even though our patients are mainly referred from two major Oncology University Clinics in Naples (and from other smaller Oncology services in the Naples area), this is a cardiologic-monocentric descriptive analysis. In addition, patients were treated with very heterogeneous therapies, and different forms of cancer were included. In our study, cancer type distribution does not completely overlap cancer type distribution in Italy, being our population mostly composed of elderly patients with colorectal cancer. In particular, only 27.7% of patients were treated with anthracyclines, and this percentage was similar among all groups of patients.

In addition, we only collected scattered data regarding the biochemical and biohumoral characteristics of the patients at the start of the study, such as troponin levels or natriuretic peptides; hence, we could not correlate them to prognosis.

In spite of these limitations, our Cardio-Oncology unit is the largest in Southern Italy and, to our knowledge, this is the first prospective study addressing these challenges in our geographic area. Our study suggests that patients at higher CV risk are more likely to have CV events. These events are significantly lower in the cohort of patients who were referred to our Cardio-Oncology unit before starting oncologic treatments, considering also that Type 1 and Type 2 patients did not differ in terms of CV risk factors. Additionally, Cox regression analyses performed for each type of patients did not show higher incidence of worse outcome with Stage IV cancer disease (*Table 4*).

These results support strict follow-up in high CV risk patients. Correcting CV risk factors and titration of therapy is fundamental for these patients before starting oncologic treatment. Furthermore, as evidenced from Supporting Information, *Figure S1*, despite CV comorbidities, EF did not worsen in these subgroups. On the opposite, we even saw a slight but statistically significant EF improvement in Types 2b and 3a. Specifically, patients with worse LVEF at the first visit experienced a more significant benefit from our CV treatment. This further supports the importance of assessing CV issues with strict CV follow-up in cancer patients.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. General characteristics of the study population at the first cardiologic assessment, including cancer types, cancer staging, and antineoplastic treatments, according to 6 Types.

Table S2. Modifications of CV treatments in the study population during follow-up according to 6 Types

Figure S1. Box plot showing the comparison of left ventricular ejection fraction between baseline and last available echocardiographic evaluation **A)** according to 3 patients types, **B)** according to 6 patients types.

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