ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) **30**, 1941–1949
https://doi.org/10.1093/eurjpc/zwad210

FULL RESEARCH PAPER
Cancer

Cardiovascular adverse events and prognosis in patients with haematologic malignancies and breast cancer receiving anticancer agents: Kurume-CREO Registry insights

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Received 9 April 2023; revised 16 June 2023; accepted 18 June 2023; online publish-ahead-of-print 23 June 2023

Aims Cancer treatment–related cardiovascular toxicity (CTR-CVT) is a growing concern in patients undergoing anticancer therapy. The Heart Failure Association (HFA) and International Cardio-Oncology Society (ICOS) risk assessment tools have been proposed for the baseline cardiovascular (CV) risk stratification of patients with cancer. This study investigated the incidence of CV adverse events in clinical practice, also using the HFA-ICOS risk tool.

Methods and results This single-centre, prospective, observational study was conducted at Kurume University Hospital from October 2016 to August 2021, including patients aged ≥20 years with haematologic malignancies or breast cancer who were receiving anticancer agents. Cardiovascular assessments were performed at enrolment and every 6 months until August 2021, with additional assessments for suspected CV adverse events. The primary endpoint was common terminology criteria for adverse events v4.0 Grade ≥2, and the secondary endpoints were all-cause and CV deaths. Of the enrolled 486 patients, CV adverse events occurred in 24.5, 15.8, 38.1, and 18.0% of patients with leukaemia, malignant lymphoma, multiple myeloma, and breast cancer, respectively. Patients at high or very high risk had a significantly higher incidence of CV events, according to the HFA-ICOS risk tool. Cardiovascular death occurred in 4 (0.8%) patients during follow-up.

Conclusion This study revealed that 16–38% of patients with haematologic malignancies and breast cancer developed CTR-CVT during follow-up, in which patients with high/very high risk were well predicted by the HFA-ICOS risk assessment tool. Monitoring and managing CV risk factors are essential for safe cancer therapy.

Lay summary As the elderly population grows worldwide, cancer and cardiac diseases have become the leading causes of death in many countries, including Japan. With advances in cancer treatment, survival rates have improved, resulting in an increasing number of cancer survivors developing therapy-related cardiovascular (CV) problems. The study, conducted at Kurume University Hospital, examined 486 participants with haematologic malignancies and breast cancer. The result demonstrates CV adverse events in 12, 45, 24, and 16 patients with leukaemia, malignant lymphoma, multiple myeloma, and breast cancer, respectively. Heart failure and left ventricular systolic dysfunction were the most common adverse events. This study demonstrates the importance of monitoring patients with cancer for potential CV risks and highlights the need for further research to improve treatment protocols for those at higher risk.

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Key findings include

- This prospective study conducted in Japan revealed a high incidence of adverse cardiovascular (CV) events in patients with haematologic malignancies and breast cancer treated with anticancer agents but a low CV mortality rate during the mid-term follow-up period.
- Patients at high/very high risk, as determined by the Heart Failure Association-International Cardio-Oncology Society risk assessment tool, experienced a higher incidence of CV events and heart failure compared with those at low and moderate risks.

Keywords Cardio-oncology • Adverse cardiovascular event • Haematologic malignancies • Breast cancer • Anthracyclines • Human epidermal growth factor receptor 2 (HER2)-targeted therapies

Introduction

In a growing population of elderly people worldwide, the leading cause of death is cancer, followed by heart disease in Japan, both of which increase with age.[1] In such situations, the coexistence of cancer and cardiovascular (CV) diseases in the elderly poses a major clinical problem.[2,3] Previously, patients with cancer were not able to live long enough to manifest long-term CV complications. However, improved survival rates among patients with cancer in recent times have raised concerns of increased CV prevalence with cancer treatment.[4,5] This concern arises from the observation that some cancer survivors develop CV problems related to anticancer therapy. Furthermore, previous studies have noted CV toxicity resulting from anthracyclines and human epidermal growth factor receptor 2 (HER2)-targeted therapies. However, CV events are increasingly reported with new agents, such as molecularly targeted drugs or immune checkpoint inhibitors.

Although new anticancer drugs have improved the prognosis of patients with cancer, CV adverse events caused by these drugs may result in dose reductions or cancer therapy interruption, both of which reduce the cancer treatment quality. Hence, the Cardio-Oncology Study Group of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), in collaboration with the International Cardio-Oncology Society (ICOS), has recently proposed a baseline CV risk stratification proforma, the HFA-ICOS risk assessment tool. The tool assesses patients with cancer prior to receiving anticancer agents with potential CV toxicity and recommends follow-up strategies for each risk.[5] The HFA/ICOS tool is presented as an expert opinion, but it has not been adequately validated.

To date, no prospective real-world clinical data have been reported on the incidence and outcomes of cancer treatment-related (CTR) CV adverse events.[2] Cardiovascular adverse events could be underestimated during the observation periods of clinical trials.[6] Therefore, we developed the Kurume University Cardio-Renal Oncology (Kurume-CREO) registry, in which we prospectively registered patients with haematologic malignancies and breast cancer, the most important type of cancer in the field of cardio-oncology. This study examined the incidence of CTR CV adverse events in clinical practice, also using the HFA-ICOS risk tool.

Methods

Study design

The Kurume-CREO registry (UMIN000024278) is a single-centre, prospective observational study conducted to examine CV adverse events in patients with haematologic malignancies and breast cancer who were scheduled for anticancer therapy at Kurume University Hospital.

The Ethics Committee of Kurume University Hospital approved this study (approval no. 16100), and all study participants provided written informed consent. The study was conducted following the ethical principles outlined in the Declaration of Helsinki.

Study population and protocol

This study enrolled patients with haematologic malignancies and breast cancer aged ≥20 years who meet the selection criteria. Our inclusion criteria were as follows: (i) age of ≥20 years, (ii) presence of haematologic malignancies or breast cancer that is or will be treated with anticancer agents at Kurume University Hospital, and (iii) provision of written informed consent for study participation. Exclusion criteria were as follows: (i) a follow-up period of ≤30 days, (ii) a predicted life expectancy of ≤6 months, and (iii) no anticancer agent treatment during the study period. This study included patients with a history of cancer, anticancer therapy, radiation therapy, or known CV diseases.

We enrolled all consecutive patients with haematologic malignancies and breast cancer scheduled for potentially cardiotoxic anticancer agents who were referred by oncologists to the Cardiology Unit of Kurume University Hospital from October 2016 to February 2021 after obtaining written informed content and were followed up until the end of August 2021.

All the patients underwent transthoracic echocardiography, 12-lead electrocardiography, chest radiography, blood sampling, and urinalysist at enrolment. All tests except echocardiography were performed every 6 months during the follow-up period. The attending haematologists and breast surgeons determined the oncological treatment strategy. Patients visited the Cardiology Unit of Kurume University Hospital when clinical signs of suspected CV events or abnormal signs were observed every 6-month examination, as described in Supplementary material online, *Figure S1*. Then, attending cardiologists performed echocardiography, lower-extremity venous ultrasonography, coronary angiography, or computed tomography, as necessary. All patients were followed up in oncology clinics, and CV events that occurred during the study period were treated and evaluated according to cardiology guidelines.[7,8]

Data collection

This study collected clinical variables, including age, sex, vital signs, CV risk factors, CV medication, previous cancer treatments, and current cancer diagnosis. Blood samples were also collected to measure N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, high-sensitivity troponin I (hs-TnI) levels, blood cell counts, and serum biochemical analyses. The blood samples were analysed at the central laboratory of Kurume University Hospital, and hs-TnI levels were separately analysed using ADVIA Centaur XP (Siemens Healthcare Diagnostics, Tokyo, Japan), with the upper normal limit set at the 99th percentile (female: 39.59 pg/mL; male: 58.05 pg/mL).

Transthoracic echocardiography was performed following current guidelines by certified cardiac sonographers using a commercially available ultrasound system such as [Vivid E90/S70 (GE Healthcare) or EPIQ 7G/EPIQ CVx (Philips)].[9,10] The left ventricular ejection fraction (LVEF) was measured using the 2D modified Simpson's method. The stroke volume was calculated by measuring the left ventricular (LV) outflow tract velocity–time integral using pulsed-wave Doppler ultrasonography. Tricuspid annular

plane systolic excursion was evaluated using an apical four-chamber right ventricular focused view in M-mode.

The baseline CV risk of the enrolled patients was assessed using the HFA-ICOS risk assessment tool,[11] which includes specific CV risk stratification formulas for anthracyclines, HER2-targeted therapies, vascular endothelial growth factor inhibitors, breakpoint cluster region-Abelson oncogene locus inhibitors, and multiple myeloma therapies. This model assessed the presence of prior CV disease, cardiac imaging findings, cardiac biomarkers, age, CV risk factors, prior cancer treatment, and lifestyle risk factors. Risk levels were stratified according to the ESC 2022 guideline as follows;[5] low risk, indicating no risk factors OR one moderate1 risk factor; moderate risk (M), indicating moderate risk factors with a total of 2–4 points [Moderate 1 (M1) = 1 point; Moderate (M2) = 2 points]; high risk (H), indicating moderate risk factors with a total of ≥5 points OR any high-risk factor; very high risk, indicating any very high-risk factor. The current study divided patients into three groups of 'low', 'moderate', and 'high/very high' risks.[5]

Study endpoints

The primary endpoints were the CV adverse events, defined by two or more attending cardiologists according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 Grade ≥2.[12] Individual CTCAE were grouped into heart failure (HF)/LV systolic dysfunction, acute coronary syndrome, venous thromboembolism, new arterial hypertension, atrial fibrillation, bradycardia, QT corrected interval prolongation, and pericardial effusion. The secondary endpoints were all-cause and CV deaths. The attending cardiologists evaluated all CV events during the follow-up period. Patients with pre-existing CV comorbidities who remained stable after enrolment in this study were not recorded as having any events.

Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD) or the median [interquartile range (IQR)] as appropriate and compared using the analysis of variance or the Kruskal–Wallis rank test, respectively. Categorical baseline variables are presented as frequencies (percentages) and compared using the χ^2 test or Fisher's exact test. The Kaplan–Meier method was used to estimate survival curves for follow-up events. A Cox proportional hazards model was used to compare all-cause mortality between the HFA-ICOS risk assessment groups. The threshold for statistical significance was set at *P*-values of <0.05. All statistical analyses were performed using JMP Pro 16 (SAS Institute Inc., Cary, NC, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander, which is designed to add frequently used statistical functions in biostatistics.

Results

Patient characteristics

This study initially enrolled 533 patients. After excluding 47 based on the exclusion criteria, 486 ultimately participated in this study. Among them, 397 patients had haematologic malignancies, and 89 had breast cancer (*Figure 1*). The median follow-up period was 716 days (IQR: 314–1266 days). *Figure 1* shows the details of the

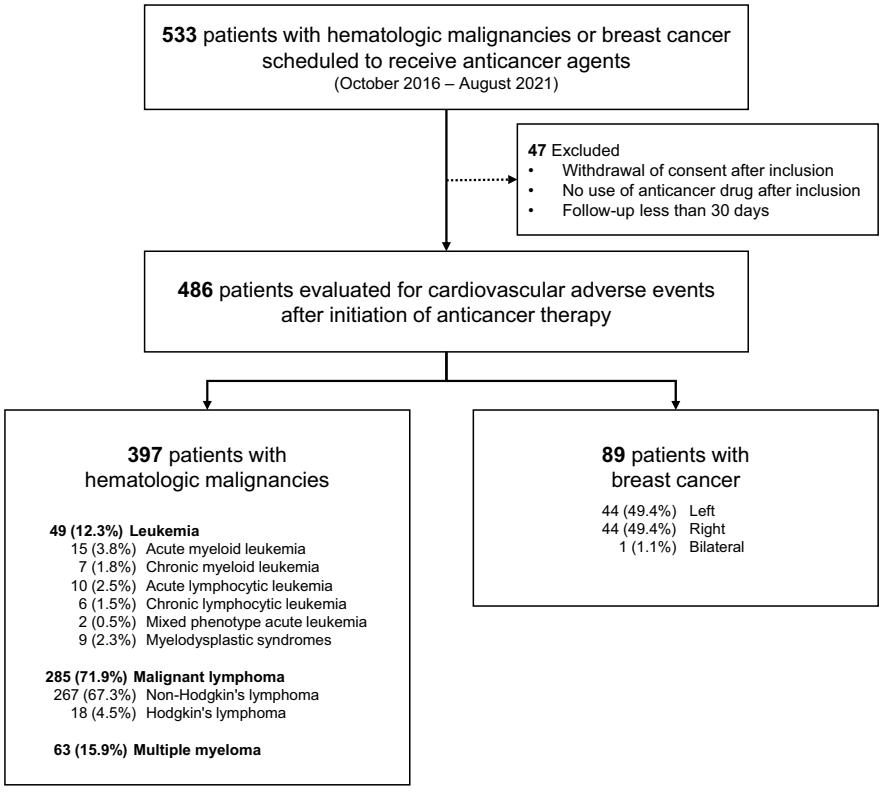

Figure 1 Patient selection flowchart and cancer diagnosis of eligible patients. Of the initial 533 patients, 47 were excluded because of withdrawal, <30 days of follow-up, or not receiving anticancer agents, thereby leaving 486 patients (397 with haematologic malignancies and 89 with breast cancer) for analysis. Non-Hodgkin lymphoma was the most common (67.3%), followed by multiple myeloma (15.9%), Hodgkin lymphoma (4.5%), and acute myeloid leukaemia (3.8%). Left and right breast cancer cases were equally distributed (49.4% each), with one bilateral case.

participants' cancer types. Non-Hodgkin's lymphoma (67.3%) was the most common haematological malignancy among the enrolled patients, followed by multiple myeloma (15.9%), Hodgkin's lymphoma (4.5%), and acute myeloid leukaemia (3.8%). There were equal numbers of cases of left and right breast cancer (49.4% for both) and one case of bilateral breast cancer among the enrolled participants in this study.

Table 1 shows the baseline patient characteristics. Their mean age was 63.8 ± 13.3 years, and 260 (53.5%) were females. Of them,

Table 1 Baseline characteristics of patients

	All patients (*n* = 486)	Haematologic malignancies (*n* = 397)			Breast cancer (*n* = 89)	*P*-value
		Leukaemia (*n* = 49)	Malignant lymphoma (*n* = 285)	Multiple myeloma (*n* = 63)		
Age (years)	63.8 ± 13.3	57.9 ± 15.5	65.3 ± 12.9	67.4 ± 8.9	59.5 ± 13.8	<0.001
Female	260 (53.5)	21 (42.9)	124 (43.5)	29 (46.0)	86 (96.6)	<0.001
Body mass index (kg/m^2)	22.6 ± 3.5	22.1 ± 3.3	22.4 ± 3.2	22.6 ± 3.5	23.7 ± 4.3	0.017
Systolic blood pressure (mmHg)	123.6 ± 16.5	121.7 ± 15.7	122.1 ± 16.0	124.7 ± 18.0	128.4 ± 16.7	0.013
Diastolic blood pressure (mmHg)	70.8 ± 11.7	69.5 ± 12.5	70.9 ± 11.2	70.3 ± 13.1	71.5 ± 11.8	0.802
Heart rate (b.p.m.)	77.7 ± 14.3	77.9 ± 14.3	78.0 ± 15.1	79.3 ± 14.7	75.5 ± 11.0	0.377
Medical history						
Recurrent cancer	76 (15.6)	5 (10.2)	40 (14.0)	19 (30.2)	12 (13.5)	0.007
Prior anticancer therapy	145 (29.8)	12 (24.5)	55 (19.3)	28 (44.4)	50 (56.2)	<0.001
Prior radiotherapy	40 (8.2)	2 (4.1)	11 (3.9)	9 (14.3)	18 (20.2)	<0.001
Hypertension	178 (36.6)	10 (20.4)	98 (34.3)	38 (60.3)	32 (36.0)	<0.001
Diabetes	68 (14.0)	5 (10.2)	40 (14.0)	6 (9.5)	17 (19.1)	0.313
Dyslipidaemia	97 (20.0)	7 (14.3)	60 (21.1)	12 (19.0)	18 (20.2)	0.744
Smoking	154 (31.7)	18 (36.7)	103 (36.1)	22 (34.9)	11 (12.4)	<0.001
Ischaemic heart disease	13 (2.7)	2 (4.1)	8 (2.8)	2 (3.2)	1 (1.1)	0.735
Heart failure	14 (2.9)	0 (0)	7 (2.5)	4 (6.3)	3 (3.4)	0.219
Atrial fibrillation	16 (3.3)	1 (2.0)	13 (4.6)	1 (1.6)	1 (1.1)	0.311
Stroke	14 (2.9)	0 (0)	10 (3.5)	3 (4.8)	1 (1.1)	0.304
Cardiovascular medication						
ACEi/ARBs	96 (19.8)	8 (16.3)	60 (21.1)	13 (20.6)	15 (16.9)	0.753
β-Blockers	25 (5.1)	0 (0)	19 (6.7)	4 (6.3)	2 (2.2)	0.126
Aldosterone antagonist	4 (0.8)	0 (0)	2 (0.7)	2 (3.2)	0 (0)	0.141
CCBs	114 (23.5)	5 (10.2)	59 (20.7)	26 (41.3)	24 (27.0)	<0.001
Statins	71 (14.6)	6 (12.2)	45 (15.8)	6 (9.5)	14 (15.7)	0.586
Anticoagulants	17 (3.5)	1 (2.0)	13 (4.6)	2 (3.2)	1(1.1)	0.429
Antiplatelet therapy	33 (6.8)	3 (6.1)	22 (7.7)	8 (12.7)	0 (0)	0.016
Laboratory data						
Creatinine (mg/dL)	0.80 ± 0.71	0.70 ± 0.20	0.79 ± 0.45	1.29 ± 1.63	0.57 ± 0.13	<0.001
eGFR (mL/min/1.73 m^2)	79.4 ± 28.1	87.3 ± 25.3	78.2 ± 25.3	65.4 ± 41.6	88.6 ± 20.8	<0.001
Haemoglobin (g/dL)	12.0 ± 2.8	10.7 ± 3.9	12.4 ± 2.7	10.3 ± 2.0	12.6 ± 1.6	<0.001
hs-TnI (pg/mL)	4.05 (2.50–9.27)	3.11 (2.49–6.96)	3.85 (2.49–9.11)	4.76 (3.26–10.83)	4.31 (2.53–9.58)	0.062
NT-proBNP (pg/mL)	107.1 (48.6–232.5)	123.0 (67.6–214.9)	125.4 (51.4–278.9)	129.2 (70.7–333.0)	55.30 (28.9–97.5)	<0.001
Echocardiographic findings						
LVEF 2D (%)	65.9 ± 6.4	65.8 ± 5.9	66.0 ± 6.5	66.1 ± 7.0	65.7 ± 5.7	0.974
LAD (mm)	33.9 ± 5.8	34.1 ± 5.7	33.8 ± 5.9	35.2 ± 6.2	33.4 ± 5.7	0.279
E/*A* ratio	0.9 ± 0.4	1.07 ± 0.34	0.87 ± 0.38	0.88 ± 0.42	0.95 ± 0.31	0.005
Average *E*/e′ ratio	9.0 ± 2.8	8.73 ± 2.90	8.82 ± 2.82	9.54 ± 2.29	9.50 ± 2.92	0.084
SV (mL)	68.3 ± 17.0	72.6 ± 21.2	67.2 ± 16.6	74.4 ± 16.9	64.6 ± 13.8	0.007
TRV (m/s)	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.5 ± 0.3	2.2 ± 0.3	<0.001
TAPSE (mm)	21.9 ± 3.7	24.0 ± 4.6	21.3 ± 3.4	23.3 ± 3.8	21.6 ± 2.9	<0.001

Data are presented as mean ± SD, median (IQR) and *n* (%).

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal b-type natriuretic peptide; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity.

86 (96.6%) patients had breast cancer, and 174 (43.8%) had haematological malignancies. Approximately 145 (29.8%) patients had previously undergone anticancer therapy, 40 (8.2%) had a history of radiotherapy, and 76 (15.6%) had recurrent cancer. Comorbidities included hypertension in 178 patients (36.6%) and HF in 14 (2.9%) patients. Further, 154 (31.7%) patients had a smoking history. The median NT-proBNP titre was 107.1 (IQR: 48.6–232.5) pg/mL, and the mean LVEF was 65.9 ± 6.4%. Seven (1.4%) patients had an LVEF of <50% at baseline, and all had haematologic malignancies.

Cancer treatments administered during the follow-up period are shown in Supplementary material online, *Table S1*. Anthracyclines were administered to 22 (44.9%) patients with leukaemia, 191 (67.0%) with malignant lymphoma, and 34 (38.2%) with breast cancer. Further, 53 (59.6%) patients with breast cancer received HER2-targeted therapy. All patients with multiple myeloma received immunomodulatory drugs (iMiDs), and 95.2% received proteasome inhibitors.

Cardiovascular adverse events

Supplementary material online, *Table S2* summarizes the CV adverse events defined as CTCAE Grade 2 for each disease during the follow-up period. Cardiovascular adverse events occurred in 12 (24.5%, 15 events) patients with leukaemia, 45 (15.8%, 52 events) with malignant lymphoma, 24 (38.1%, 31 events) with multiple myeloma, and 16 (18.0%, 18 events) with breast cancer (see Supplementary material online, *Table S2*). Heart failure/left ventricular systolic dysfunction, which occurred in 3 (6.1%) patients with leukaemia, 22 (7.7%) with malignant lymphoma, 12 (19.0%) with multiple myeloma, and 4 (4.5%) with breast cancer, was the most common CV adverse event. *Figure 2A–D* shows each disease's primary endpoint of CV adverse events divided by past cancer treatment status. Patients with malignant lymphoma (*Figure 2B*) had significantly worse CV adverse events in the presence of previous cancer treatment [hazard ratio (HR) 2.06, 95% confidence interval (CI) 1.10–3.87; $P = 0.025$]; however, no significant differences were observed in the other three diseases. *Figure 2E–H* show HF/LV systolic dysfunction, which is the most common CV adverse event. Patients with malignant lymphoma, multiple myeloma, or breast cancer tended to develop worse HF in the presence of previous cancer treatment (*Figure 2F–H*).

The CV risk of enrolled patients was stratified into three groups using the HFA-ICOS risk assessment tool,[11] with 215 (44.2%), 119 (24.5%), and 152 (31.3%) patients in the low-risk, moderate-risk, and high-/very high-risk groups, respectively (see Supplementary material online, *Table S3*). The incidence of the primary endpoint was predicted as 18.5, 18.5, and 29.0% in the low-risk, moderate-risk, and high-/very high-risk groups, respectively ($P = 0.003$). Kaplan–Meier curves of the primary endpoint and HF/LV dysfunction stratified by the HFA-ICOS risk group have shown significantly worse events in the high-/very high-risk group (*Figure 3*), in which the HRs in the high-/very high-risk group compared with the low-risk group were 2.34 (95% CI 1.48–3.71, $P < 0.001$) in the primary endpoint and 3.57 (95% CI 1.70–7.51, $P < 0.001$) in HF/LV dysfunction (*Table 2*). Further, the HRs in the high-/very high-risk group compared with the moderate-risk group were 1.84 (95% CI 1.10–3.08, $P = 0.020$) in the primary endpoint and 2.68 (95% CI 1.20–6.00, $P = 0.017$) in HF/LV dysfunction. No significant difference was found in the event risk between the low- and moderate-risk groups (*Table 2*).

Prognosis

During the follow-up period, all-cause death occurred in 13 (26.5%), 66 (23.2%), 21 (33.3%), and 8 (9.0%) patients with leukaemia, malignant lymphoma, multiple myeloma, and breast cancer (*Figure 4A*), with 1-year survival rates of 81.2, 85.8, 71.1, and 91.7%, respectively. Cardiac deaths were observed in four (0.8%) cases, with three (1.1%) from malignant lymphoma and one (1.6%) from multiple myeloma (*Figure 4B*). The other causes of death were originally attributed to malignancy.

Discussion

The primary findings of this study can be summarized as follows: (i) during a median follow-up of 716 days, CV adverse events were observed in 24.3, 15.8, 38.1, and 18.0% of patients with leukaemia, malignant lymphoma, multiple myeloma, and breast cancer, respectively. (ii) The incidence of CV events was significantly higher in patients classified as high or very high risk at baseline using the HFA-ICOS risk assessment tool. (iii) The 1-year survival rates were 81.2, 85.8, 71.1, and 91.7% for leukaemia, malignant lymphoma, multiple myeloma, and breast cancer, respectively. (iv) Only four (0.8%) patients experienced CV death. To our knowledge, this is the first study to prospectively investigate anticancer agent-related CV adverse events in Japanese patients with haematologic malignancies and breast cancer, and it is also the first to investigate the validity of the HFA-ICOS risk assessment tool in the majority of haematologic malignancies.

Increase in cardiovascular diseases and cancer

Japan has the most elderly population among developed countries, and the number of cancer patients in Japan is expected to reach 3.5 million by 2025.[13] Furthermore, the total number of Japanese cancer patients with CV disease was 253 000 in 2015 and will reach 313 000 by 2030–34.[14] Recent therapeutic developments in cancer have steadily decreased cancer-related mortality and consequently increased the number of cancer survivors. Cardiovascular diseases and cancer have common risk factors (smoking, obesity, diabetes, alcohol, hypertension, hyperlipidaemia, etc.), and their co-occurrence is increasing with the aging population.[15,16] Hence, the increasing importance of CTR CV toxicity (CTR-CVT) underscores the need for close collaboration between cardiologists and oncologists.[5,17]

A history of CV disease may influence the choice of cancer treatment; however, anticancer agents can cause CV toxicity, affecting current cancer treatment. Additionally, the potential impact of cancer treatment on the CV risk may negatively affect cancer survival.[18] Thus, most clinical trials on anticancer agents have excluded patients with CV risks, which increased the possibility of underestimating the CV hazards of anticancer drugs, in addition to inadequate CV safety monitoring. A recent CV safety report indicated that patients with CV conditions, mainly HF, were excluded in 42 (84%) of 50 Phases 2 and 3 clinical trials on breast cancer, and that 23 (46%) of these trials did not report CV safety assessments.[19] Further, any of the trials reported no natriuretic peptide and troponin levels.[19] The early detection and management of CTR-CVT require CV risk stratification associated with cancer treatment and epidemiological data accumulation in real-life clinical practice.

Cardiovascular toxicity by anticancer agents

Cancer treatments have recently changed. First, an improved understanding of the mechanisms of anticancer treatment toxicity can allow the identification of novel targets to reduce CV complications while providing biological insights into CV pathophysiology and informing new platforms for drug discovery.[20] Next, cardiologists and oncologists will work closely to assess CV risk, minimize vascular toxicity, and manage long-term adverse effects.[20] Cancer therapy can be shifted from non-selective toxicants, such as anthracyclines, to therapies that target specific pathways important for cancerous tissue growth and survival. The field of cardio-oncology initially emerged as a specialty for HF due to toxicity from traditional drugs such as anthracyclines and trastuzumab; however, concerns about CV side effects from other anticancer agents, such as molecularly targeted drugs and immune checkpoint inhibitors, have increased in recent years.[21] Several large-scale trials of combination therapies for multiple myeloma, including proteasome

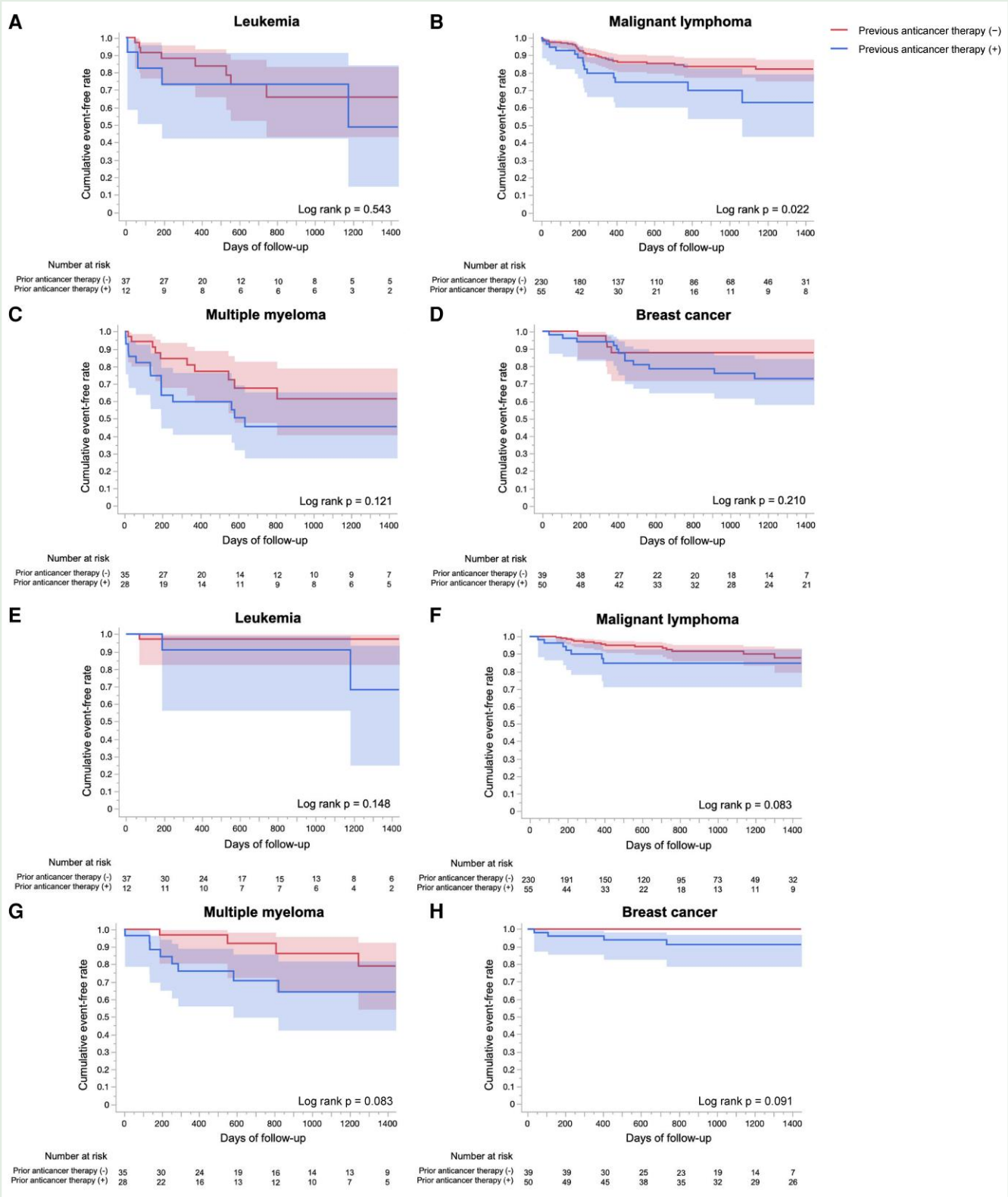

Figure 2 Overall adverse cardiovascular events and heart failure/left ventricular systolic dysfunction events. Kaplan-Meier curves showing event-free survival rates for cardiovascular adverse events (*A–D*) and heart failure/left ventricular systolic dysfunction events (*E–H*) in patients with leukemia, malignant lymphoma, multiple myeloma, and breast cancer. Blue and red shades indicate 95% confidence intervals for patients with and without previous anticancer therapy, respectively.

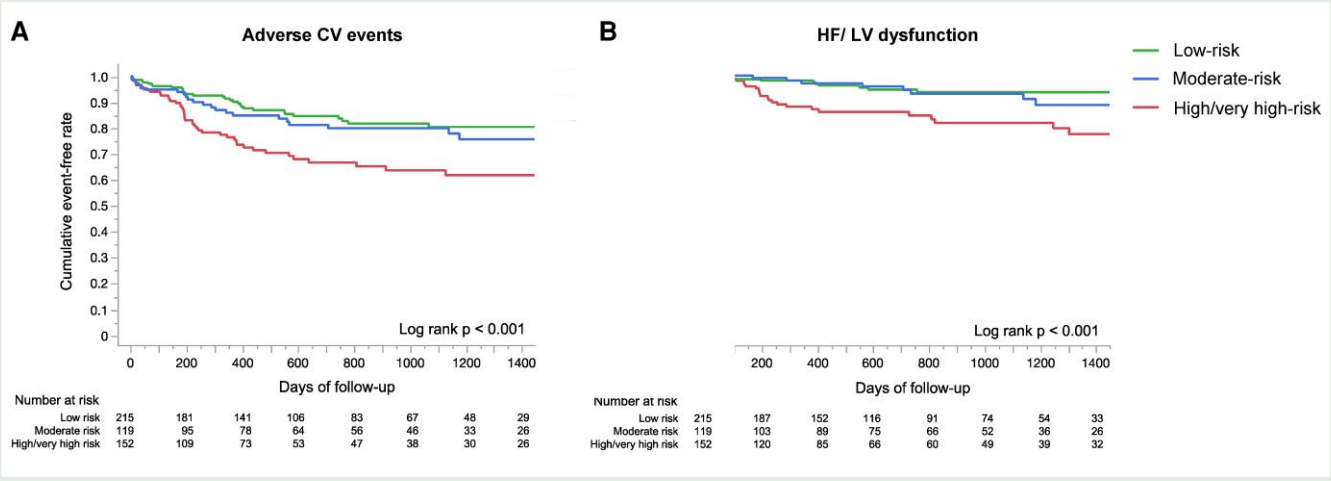

Figure 3 Incidence of adverse cardiovascular events and heart failure/left ventricular dysfunction stratified by Heart Failure Association-International Cardio-Oncology Society risk assessment tool. Kaplan-Meier curves showing event-free survival for adverse cardiovascular events (*A*) and heart failure/left ventricular dysfunction (*B*), stratified by baseline cardiovascular risk using the HFA-ICOS risk assessment tool. HF, heart failure; LV, left ventricular; HFA-ICOS, Heart Failure Association-International Cardio-Oncology Society.

Table 2 Association between baseline Heart Failure Association-International Cardio-Oncology Society risk assessment and adverse cardiovascular events and heart failure/left ventricular dysfunction

Baseline HFA-ICOS risk assessment	All CV events (CTCAE Grade ≥2)		Heart failure/LV dysfunction (CTCAE Grade ≥2)	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Moderate risk vs. low risk	1.27 (0.73–2.19)	0.395	1.33 (0.53–3.38)	0.545
High/very high risk vs. low risk	2.34 (1.48–3.71)	<0.001	3.57 (1.70–7.51)	<0.001
High/very high risk vs. moderate risk	1.84 (1.10–3.08)	0.020	2.68 (1.20–6.00)	0.017

CTCAE, common terminology criteria for adverse events; CV, cardiovascular; HFA-ICOS, Heart Failure Association–International Cardio-Oncology Society; LV, left ventricular.

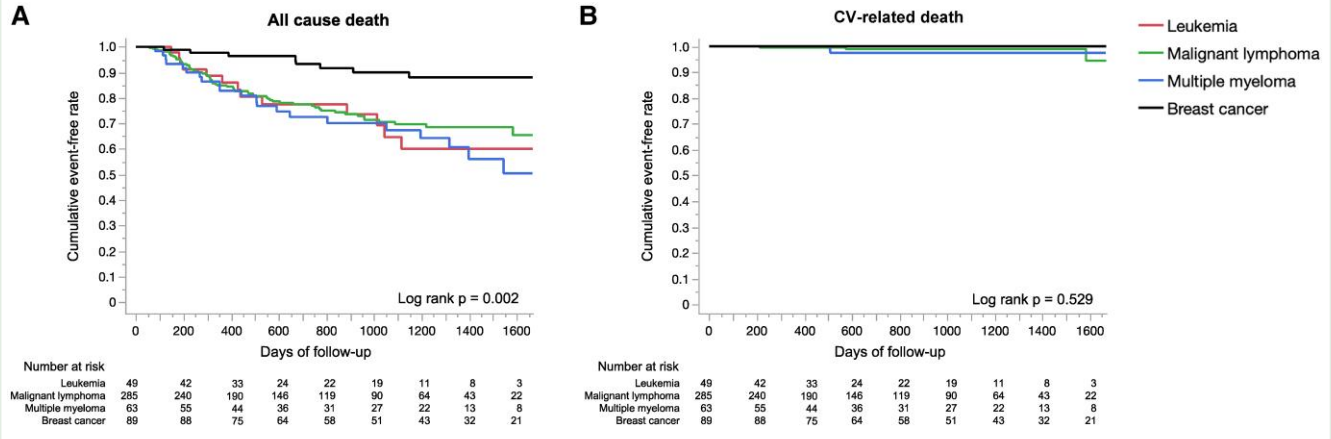

Figure 4 Mortality rates among different disease groups. Kaplan–Kaplan-Meier curves showing all-cause death (*A*) and cardiovascular death (*B*) due to leukemia, malignant lymphoma, multiple myeloma, and breast cancer. CV, cardiovascular.

inhibitors and iMiDs, have shown an increased risk of serious CV adverse events,[22,23] and indeed, the current study has revealed that CV adverse events were more common among patients with multiple myeloma.

Effective stratification of baseline CV risks in cardio-oncology management is expected to identify patients who will benefit the most from CV monitoring and prevention. Real-world clinical practice often involves cancer patients with complex CV risk profiles in contrast to clinical trials of anticancer agents, which often focus on patients with low CV risk. Data validating the HFA-ICOS risk assessment tool in real-world settings have been reported for patients with chronic myeloid leukaemia and breast cancer patients;[24,25] however, more evidence is required. This study classified 24.5% of patients as moderate risk and 31.3% as high or very high risk according to the HFA-ICOS risk assessment tool, and patients classified as high or very high risk using the HFA-ICOS risk tool had a significantly higher incidence of CV events. However, no significant differences were observed between moderate- and low-risk patients in CV event occurrence. These findings demonstrate the potential for a more appropriate allocation of scarce CV resources, indicating the possibility of focusing cardio-oncology resources on the high-/very high-risk group. Meanwhile, a multidisciplinary approach involving physical training, lifestyle counselling, control of CV risk factors, and psychological support is strongly recommended for cancer patients, regardless of their CV risk levels.[26,27] Further large-scale validation should be conducted considering the balance of available medical resources in clinical settings.

Causes of death among patients with cancer

Several population-based studies have reported the risk of CV death as the highest in the first year after cancer diagnosis.[28–30] However, the present study reported a lower risk of CV death during the ∼2-year follow-up period compared with a higher incidence of CV events. Directly comparing the present study with these studies was impossible because population-based studies often do not include precise cancer treatments or other medical histories, and periodic CV assessments may be impossible in population-based studies. Furthermore, the present study prompted more aggressive interventions by cardiologists, which may have resulted in fewer CV deaths. The recently published CARDIOTOX registry,[31] a prospective study on patients treated with anticancer agents at high risk of cardiotoxicity, revealed myocardial damage/functional failure in 37.5% of patients. However, the prevalence of serious cardiotoxicity affecting prognosis was low, probably due to the exclusion of patients with a history of HF or severe LV disease.[31] Further, this may have been affected by the study design. The CARDIOTOX registry and the present study revealed that cardiologists evaluated the CV risks in asymptomatic patients with cancer, which might potentially prevent CV events and improve patient prognosis. Unfortunately, this issue cannot be avoided due to the nature of this registry. An international prospective registry on cardio-oncology has recently been initiated among patients with breast cancer, haematological malignancies, and immune checkpoint inhibitor treatment (Global Cardio-Oncology Registry).[32] Notably, racial differences may exist in the incidence of CTR-CVT,[33] and this study can hopefully help elucidate the risk factors for CTR CV disease in various geographical regions and demographic populations.

Limitations

This study had several limitations. First, this was a single-centre study conducted at a tertiary care university hospital with a relatively small sample size; thus, some degree of bias may have existed. Second, echocardiography was only required at baseline, and further testing was not performed unless the patients were symptomatic or had biomarker abnormalities, electrocardiography, or chest X-ray findings. Thus, the incidence of asymptomatic cancer therapy–related cardiac dysfunction (CTRCD), which was defined by the 2022 ESC cardio-oncology guidelines, may have been underestimated.[5] Third, Global Longitudinal Strain was not obtained as a routine echocardiographic parameter, which might have underestimated mild asymptomatic CTRCD incidence as defined by the latest ESC guidelines.[5] Finally, the study did not examine the relationship between the type of anticancer agents used and the occurrence of CV events, which is the focus of our next project.

Conclusions

This prospective study conducted in Japan revealed that CTR-CVT occurs in the majority of haematologic malignancies and breast cancer treated with anticancer agents, in which high-/very high-risk patients were well predicted by the HFA-ICOS risk assessment tool. Conversely, CV mortality was found to be low during the medium-term follow-up. These results provide important information on the need for comprehensive CV follow-up, although developing CV surveillance strategies in cardio-oncology is controversial. Anticancer therapy discontinuation due to CV events should be avoided.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

The authors thank Yui Kageyama, Mami Nakayama, Hiroki Aoki, Saki Hirakata, Satoko Ohno, Masanori Otsuka, Mika Enomoto, Ako Fukami, and Junichi Shibata for their contributions to this study.

Authors' contributions

T.S.: conceptualization, methodology, formal analysis, data curation, and writing-original draft preparation. S.N.: methodology, investigation, writing-review and editing. N.M.: methodology, data curation, and formal analysis. K.S.: investigation. S.I.: investigation. R.S.: investigation and conceptualization. U.T.: supervision and conceptualization. K.N.: supervision and conceptualization. K.F.: supervision and conceptualization. Y.F.: project administration, conceptualization, writing-review and editing. All authors have read and approved the final article.

Funding

This study was funded by the Kimura Memorial Heart Foundation Research Grant of 2016.

Conflict of interest: T.S. has received honoraria from Novartis Pharmaceuticals KK and Otsuka Pharmaceuticals Co. Ltd. Y.F. received a research grant from Sanofi KK and Shionogi & Co., Ltd, honoraria from AstraZeneca KK, Eisai Co., Ltd, and Kowa Pharmaceutical Co., Ltd, research grants and honoraria from MSD KK, Otsuka Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Sumitomo Pharma Co., Ltd, Teijin Pharma Ltd, Bayer Yakuhin, Ltd, Mochida Pharmaceutical Co., Ltd, Astellas Pharma Inc, Sanwa Kagaku Kenkyusho Co., Ltd, Takeda Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Corp., Pfizer Japan Inc., Ono Pharmaceutical Co., Ltd, and AstraZeneca KK. All other authors have no conflicts of interest relevant to the contents of this article to disclose.

Data availability

The data underlying this article will be shared with others to reproduce results or replicate procedures upon reasonable request to the corresponding author, subject to institutional and ethics committee approval.

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