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Original Article

Prospective screening for myocarditis in cancer patients treated with immune checkpoint inhibitors

Asuka Furukawa (MD, PhD) [a,b,1], Yuichi Tamura (MD, PhD, FJCC) [a,b,*,1], Hirohisa Taniguchi (MD, PhD) [a], Akio Kawamura (MD, PhD) [b], Seisuke Nagase (MD, PhD) [c], Aeru Hayashi (MD, PhD) [d], Yuichiro Tada (MD, PhD) [e], Kazuhiro Sase (MD, PhD) [f], Kiyohiko Hatake (MD, PhD) [g]

[a] Department of Cardiology, International University of Health and Welfare Mita Hospital, Tokyo, Japan
[b] Department of Cardiology, International University of Health and Welfare School of Medicine, Narita, Japan
[c] Department of Thoracic Oncology, International University of Health and Welfare Mita Hospital, Tokyo, Japan
[d] Department of Thoracic Surgery, International University of Health and Welfare Mita Hospital, Tokyo, Japan
[e] Department of Head and Neck Oncology and Surgery, International University of Health and Welfare Mita Hospital, Tokyo, Japan
[f] Department of Clinical Pharmacology, Juntendo University, Tokyo, Japan
[g] Department of Hematology, International University of Health and Welfare Mita Hospital, Tokyo, Japan

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) improve clinical outcomes in various cancers, but sometimes induce autoimmune adverse effects, including myocarditis, which is the most serious complication. There are many reports on ICI-induced myocarditis; however, only a few prospective surveillance reports exist. Therefore, we developed a prospective screening protocol and performed monitoring clinically suspected myocarditis in every patient treated with ICIs.

Methods: We prospectively enrolled 126 consecutive patients treated with ICIs in this cohort. Outcomes of patients were determined and analyzed between April 2017 and May 2020. We evaluated vital signs, biomarkers, electrocardiograms, chest radiographs, and echocardiographs before and at 7 ± 3, 14 ± 3, 21 ± 3, and 60 ± 7 days after ICI initiation.

Results: Eighteen (14.3 %) presented troponin I elevation and 13 of them presented signs of clinically suspected myocarditis (10.3 %). Among the 13 patients, ICI was discontinued in four cases (3.2 %) without fatal events. Myocarditis appeared at an early stage of ICI treatment, regardless of severity (median, 44 days).

Conclusions: We observed the frequency of patients with myocarditis or myocardial damage through a prospective screening program in the real world. Although the frequency was higher than expected, most cases were mild and ICI treatment could be continued under careful observation.

Introduction

Immune checkpoint inhibitors (ICIs) significantly improved clinical outcomes in various cancers and have been approved for a growing number of cancers. Consequently, they are being used more frequently, including in first-line treatment. On one hand, ICIs enhance anti-tumor immunity, while on the other hand, they can induce autoimmune effects on normal tissues. Such adverse events, called immune-related adverse events (irAEs), have a different profile than those caused by conventional anticancer agents and have been reported to cause autoimmune-like damage to various organs.

A retrospective analysis using VigiBase, the World Health Organization's global database, reported that myocarditis occurred in 0.41 % of patients treated with ICIs alone and 1.33 % of patients treated with a combination of ICIs, suggesting a higher risk of using ICIs in combination [1]. The median time from the first administration of an ICI to the onset of myocarditis was 30 days (18–60 days), which was noted in the early stages of treatment. In addition, a fatality rate of approximately 50 % has been reported for patients with myocarditis, making it the most lethal complication at the time of onset. Therefore, myocarditis is a complication to be aware of and needs to be recognized as soon as possible. Actually, we had faced two cases of fatal myocardial injury as well; the days between initiation of treatment and appearance of myocardial injury were short; initial symptoms, such as general malaise and

* Corresponding author at: Department of Cardiology, International University of Health and Welfare Mita Hospital, 1-4-3, Mita, Minatoku, Tokyo, 108-8329, Japan.
E-mail address: tamura.u1@gmail.com (Y. Tamura).
[1] Asuka Furukawa and Yuichi Tamura contributed equally.

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respiratory distress, were nonspecific; and sudden death occurred due to refractory ventricular arrhythmias. These cases are similar to previously reported ICI-related myocarditis cases.

However, most of the available evidence is case reports, case series, or retrospective studies, which may be flawed by reporting bias. While the clinical presentation of ICI-associated myocarditis can vary from asymptomatic elevations in cardiac biomarkers to severe clinical signs and symptoms [2], only the most severe cases have tended to be reported, and asymptomatic or mildly symptomatic cases may have not been identified or gone unreported. In this context, the incidence of ICI-related myocarditis with subtle symptoms is still unknown, and the course of untreated myocarditis is also unknown.

Therefore, it is important to perform prospective screening to determine the incidence and features of findings suggestive of myocarditis. In this study, we developed a structured screening program, and prospectively monitored all patients treated with ICIs at our institution.

Methods

Screening protocols and the definition of test abnormalities

In this study, we prospectively evaluated all cancer patients treated with ICIs at the International University of Health and Welfare Mita Hospital, Minato-ku, Tokyo, Japan, between April 2017 and May 2020. This study was approved by the ethics committee of the Faculty of Medicine at International Health and Welfare University (approval no.: 5-18-8) and followed the standards of the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation. The practical protocol for screening of myocardial disorders is shown in Fig. 1. This protocol included the evaluation of vital signs, blood samples [troponin-I, creatine kinase (CK), brain natriuretic peptide (BNP), D-dimer], electrocardiograms (ECGs), chest radiographs, and echocardiographs. All examinations, except for echocardiography, were performed before initiating ICI treatment and at 7 ± 3, 14 ± 3, 21 ± 3, and 60 ± 7 days after ICI initiation. Echocardiography was performed before ICI administration as well as 7, 21, and 60 days after ICI administration. All evaluations were continued at 3-month intervals thereafter. Since we retrospectively evaluated the outcomes of the prospective screening program, the opt-out method was used to obtain consent from the patients for the data.

High-sensitivity troponin-I elevation was defined as the value above the upper limit of normal (26.2 pg/ml) and more than double the baseline, and CK elevation was graded according to Common Terminology Criteria for Adverse Events (CTCAE) (ver. 5.0). BNP elevation was defined as >100 pg/mL and more than double the baseline. Left ventricular dysfunction was defined as resting ejection fraction <53 % and ≥10 % drop from the baseline. Global longitudinal strain decrease was defined as ≥15 % drop from the baseline, and hypertension was defined as CTCAE grade 3 or higher. High-sensitivity troponin-I was measured by Abbott Architect (Abbott Diagnostics, Abbott Park, IL, USA).

Since troponin is a potent screening tool as a biomarker for myocarditis, we checked for other findings in our protocol to confirm the presence of myocarditis when troponin-I was positive.

Definition of clinically suspected myocarditis

Myocarditis was diagnosed based on a guideline-recommended scoring system for myocarditis [3] that incorporates selected variables, including the clinical, biomarker, and imaging features.

Additionally, in cases with elevated troponin-I, clinically suspected myocarditis was diagnosed when any of the following was observed as well: 1) ≥1 clinical presentation; 2) if asymptomatic, but ≥1 diagnostic criteria, including ECG/Holter/stress test features, functional and structural abnormalities on cardiac imaging [echocardiography/angiography/cardiovascular magnetic resonance (CMR)], or tissue characterization by CMR, were met.

Statistical analysis

The continuous variables are described as mean ± standard error. Additionally, on the basis of normality, comparisons were made using the Student's *t*-test. Categorical variables are presented as percentages, and χ^2 tests were used. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Inc., Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$.

Results

Patient characteristics

This prospective analysis included the screening of 126 consecutive patients using a defined protocol at the International Medical Welfare University Mita Hospital Cardio-Oncology Unit from April 2017 to May 2020.

The mean patient age was 64.0 ± 1.2 years, and 69.0 % of patients were male (Table 1). Carcinoma varied according to the indications for each ICI, but, overall, head and neck cancer was the most common cancer (55.6 %), followed by lung cancer (33.3 %), gastrointestinal

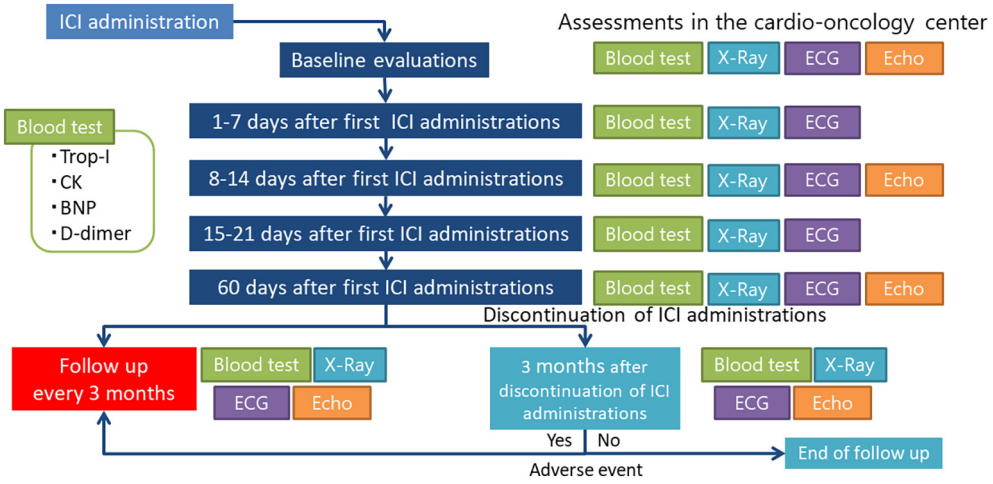

Fig. 1. Prospective screening protocol for myocarditis in cancer patients receiving immune checkpoint inhibitor therapy.
BNP, brain natriuretic peptide; CK, creatine kinase; ECG, electrocardiogram; Echo, echocardiogram; ICI, immune checkpoint inhibitor; Trop-I, troponin-I; X-Ray, chest x-ray.

Table 1
Characteristics of patients treated with ICI in the prospective screening program.

	Total (n = 126)	Nivolumab (n = 75)	Pembrolizumab (n = 27)	Atezolizumab (n = 19)	Durvalumab (n = 5)
Age (years)	64.0 ± 1.2	61.1 ± 1.5	68.0 ± 2.4	68.2 ± 3.3	71.0 ± 3.3
Gender (Male), n (%)	87 (69.0)	51 (68.0)	18 (66.7)	13 (68.4)	5 (100.0)
Type of carcinoma: Lung, n (%)	42 (33.3)	5 (6.7)	15 (55.6)	17 (89.5)	5 (100.0)
Head and neck, n (%)	70 (55.6)	62 (82.7)	8 (29.6)	0	0
Urinary organ, n (%)	5 (4.0)	3 (4.0)	2 (7.4)	0	0
Digestive organ, n (%)	6 (4.8)	5 (6.7)	1 (3.7)	0	0
Breast, n (%)	2 (1.6)	0	0	2 (10.5)	0
Sarcoma, n (%)	1 (0.8)	0	1 (3.7)	0	0
History of heart disease, n (%)	38 (30.2)	23 (30.7)	10 (37.0)	3 (15.8)	2 (40.0)
Prior chest irradiation, n (%)	36 (28.6)	16 (21.3)	4 (5.3)	11 (57.9)	5 (100.0)
Anthracycline, n (%)	4 (3.2)	0	0	4 (21.1)	0

ICI, immune checkpoint inhibitor.

cancer (4.8 %), urological cancer (4.0 %), breast cancer (1.6 %), and sarcoma (0.8 %). Previous cardiovascular disease, previous chest radiotherapy, and anthracycline treatment were present in 30.2 %, 28.6 %, and 3.2 % of the cases, respectively.

Description of the test abnormality

Table 2 shows the frequency of abnormal values for each parameter and the number of irAEs associated with ICI treatment. Forty-six patients (36.5 %) within this prospective screening cohort presented with abnormal findings in at least one of the cardiovascular examinations, and the median time to onset was 21 days after ICI administration (the details of abnormal findings are shown in Table 2). Regarding ECG abnormalities, conduction disturbances were one type of non-lethal complication observed at a relatively higher rate (5.6 %). Echocardiography showed few cases (2.4 %) of left ventricular dysfunction. Elevated troponin I was observed in 18 cases (14.3 %) (Fig. 2).

Frequency and severity of clinically suspected myocarditis

As mentioned in the methods section, myocarditis was assessed according to the European Society of Cardiology (ESC) guidelines [3].

Table 2
Abnormalities in the cardiovascular screening examinations (n = 126).

	N	Median days after administration of ICI [Min–Max]
Biomarker abnormalities		
CK elevation	12	32 [8–89]
BNP elevation	11	23 [5–113]
Troponin-I elevation	18	26.5 [3–159]
Electrocardiogram findings		
Cardiac conductive disorders	7	17 [1–91]
Nonspecific ST-T wave changes	10	14 [2–44]
Frequent PACs	3	52 [33–117]
Frequent PVCs	6	12 [0–51]
Non-sustained ventricular tachycardia	1	0
Supraventricular tachycardia	3	31 [30–48]
Sinus tachycardia	2	55.5 [2–109]
QT prolongation	1	234
Echocardiogram findings		
Increased of pericardial effusion	2	10 [6–14]
Left ventricular wall thinning	1	34
Left ventricular dilatation	1	151
Worsening of tricuspid regurgitation	2	11.5 [9–14]
Left ventricular dysfunction	3	109 [3–530]
|GLS| decrease	4	14 [3−33]
Elevated blood pressure	1	416
Increased of pleural effusion	2	11.5 [9–14]
Venous thromboembolism	2	43.5 [41–46]

BNP, brain natriuretic peptide; CK, creatine kinase; GLS, global longitudinal strain; ICI, immune checkpoint inhibitor; PAC, premature atrial contractions; PVC, premature ventricular contractions.

Among the 18 patients who presented with troponin I elevation, 13 patients (10.3 %) had clinical presentation or met the diagnostic criteria other than troponin I. We classified the 13 patients as being clinically suspected of having myocarditis (Fig. 2). Among the 13 clinically suspected myocarditis patients, 8 patients were symptomatic (Table 3), of whom 4 (3.2 %) patients had mild symptoms and 4 (3.2 %) patients had moderate to severe symptoms associated with other test abnormalities, which required immediate discontinuation of ICI. Seven clinically suspected myocarditis patients had other irAE, including pneumonitis (n = 3), myositis (n = 1), colitis (n = 1), encephalitis (n = 1), and Guillain-Barré syndrome (n = 1). Clinically suspected myocarditis appeared at an early stage of ICI treatment regardless of severity (median, 44 days), and 84.6 % of which presented within 2 months of initiating ICI. Among the 126 patients, only 4 patients (3.2 %) discontinued ICI treatment due to myocarditis but none of them were fatal, maybe because we could intervene early. One out of the four cases received intravenous immunoglobulin and plasma exchange and steroid therapy, another received intravenous

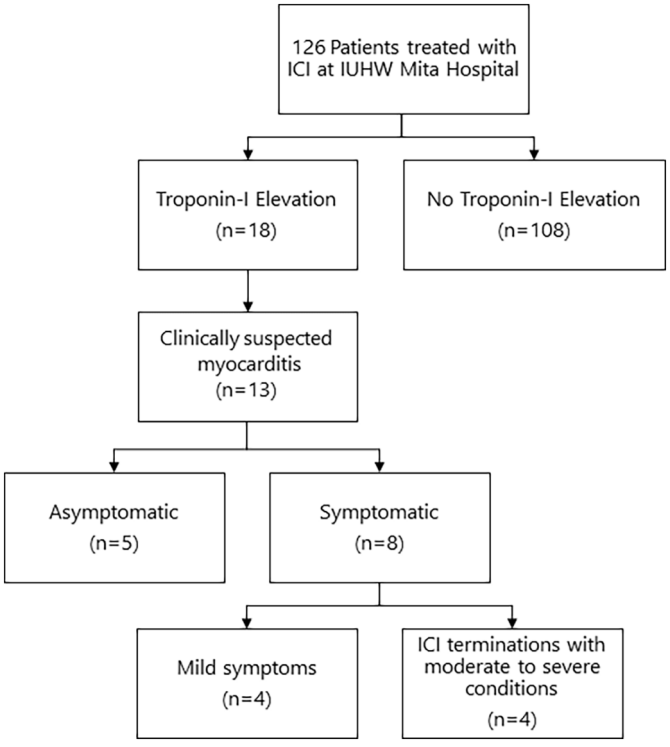

Fig. 2. CONSORT flow diagram.
ICI, immune checkpoint inhibitor; IUHW Mita Hospital, International University of Health and Welfare Mita Hospital.

Table 3
Frequency and severity of clinically suspected myocarditis with ESC guideline among patients with troponin I elevation.

		N (%)	Median days to onset [range]	ECG abnormality	Echo abnormality	Discontinuations of ICI	Number of patients with CK elevation	Median days to CK elevation [range]	Number of patients with CK elevation preceded by Trop-I elevation
Clinically suspected Myocarditis		13 (10.3 %)	44 [7–113]	11	3	4	4	22 [7–47]	4
Asymptomatic		5 (4.0 %)	48 [7–109]	4	2	0	0	NA	0
Symptomatic	Mild Symptom	4 (3.2 %)	24.5 [11−113]	3	0	0	0	NA	0
	Moderate to severe abnormal test results with immediate ICI discontinuations	4 (3.2 %)	30 [8–48]	4	1	4	4	22 [7–47]	4

CK, creatine kinase; ECG, electrocardiogram; ESC, European Society of Cardiology; ICI, immune checkpoint inhibitor; Trop-I, troponin-I.

immunoglobulin and steroid therapy, and the other two cases received steroid therapy. Interestingly, all asymptomatic cases and cases with mild symptoms were able to continue ICI with careful follow-up.

When investigating the risk factors related to abnormal values in cardiovascular examinations, we failed to find any associations with known risk factors of cardiovascular diseases (Table 4), such as a history of heart failure or coronary artery disease. Accordingly, when we investigated biomarkers for early identification of myocarditis, baseline data showed no difference between the groups with and without clinically suspected myocarditis. However, we found that none of the patients with asymptomatic and mild myocarditis had elevated levels of CK, whereas all four patients with moderate to severe myocarditis had elevated levels of CK, which preceded elevated levels of troponin I (Table 3).

Discussion

In the present study, we prospectively screened for cardiovascular events in our cohort of patients treated with ICI in the real world. We observed clinically suspected myocarditis cases more frequently than previously reported. However, most patients were asymptomatic or mild, and ICI treatments could be continued with careful follow-up. All of the moderate to severe cases required discontinuation of ICI treatment at early onset, which resulted in the avoidance of fatalities. Although there was no association between the occurrence of clinically suspected myocarditis and known cardiovascular risk factors, it was suggested that CK elevation may be expected to be an earlier predictor of severe myocarditis. In addition, most clinically suspected myocarditis cases were observed in the early stage of ICI administration, which is consistent with previous reports. To the best of our knowledge, this is the first report of a prospective evaluation of ICI-associated myocarditis.

The first point of interest is that there is a difference in the incidences of myocarditis between this prospective, all-case screening study and previous retrospective analyses. In the present study, we found that 13 of 126 (10.3 %) patients had clinically suspected myocarditis, which was mainly mild or asymptomatic. In 2016, Johnson et al. [4] first reported two cases of fatal myocarditis immediately after combination ICI therapy. Prior to this report, there were few cases of myocarditis in any clinical trial up to the ICI approval. Subsequently, using the Bristol-Myers Squibb post-marketing safety database, the incidence of acute myocarditis was reported to be 0.06 % when nivolumab was used alone and 0.27 % when nivolumab was combined with ipilimumab; with both increasing the frequency and severity of myocarditis. Since this report, the frequency of reported myocarditis cases has increased, from an initial report of 0.06 % to 0.3 % to a recent retrospective analysis showing an incidence of up to 1.14 % [1,2,4–7].

In contrast to these retrospective results, our results show a high incidence of clinically suspected myocarditis, but a low mortality rate. This is because previous reports of retrospective analysis identified only severe and/or fatal cases and ignored asymptomatic or minor cases. A recent meta-analysis of randomized clinical trials found that it was impossible to detect significant cardiotoxicity associated with the use of anti-programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) immunotherapy without proactive surveillance [8]. In the present study, we performed serial prospective examinations and evaluations of all patients treated with ICI and found a number of asymptomatic and mild cases. Therefore, this study is meaningful in that it clarifies the true incidence of clinically suspected myocarditis or myocardial damage by including the silent cases and shows that more patients treated with ICI experience myocarditis than previously thought, although only a small percentage of these cases are fatal. In addition, it is worth emphasizing that in the absence of a structured program for assessing cardiovascular events, the great majority of myocarditis events can be overlooked or misdiagnosed.

The second important point to be discussed is whether the asymptomatic or mild myocarditis found in our study has any pathological significance. Indeed, 69.2 % of the clinically suspected myocarditis found in this study were asymptomatic or mild cases. There has been a report of silent cases of ICI-associated myocarditis, in which patchy fibrosis and diffuse mononuclear cell infiltration of the myocardium were observed at autopsy, despite the absence of clinically evident myocarditis findings [9]. Moreover, Zhang et al. reported that left ventricular function was preserved in more than half (61 %) of the patients pathologically diagnosed with ICI-related myocarditis [10], suggesting that

Table 4
Clinical characteristics of patients with or without myocarditis.

	Total (n = 126)	Clinically suspected Myocarditis (+) (n = 13)	Myocarditis (−) (n = 113)	p
Age, years	64.0 ± 1.2	66.2 ± 4.7	63.8 ± 1.2	0.543
Male, n (%)	87 (69.0)	11 (84.6)	76 (67.3)	0.200
History of heart disease, n (%)	38 (30.2)	3 (23.1)	35 (31.0)	0.557
Heart Failure ≥ stage B, n (%)	31 (24.6)	2 (15.4)	29 (25.7)	0.415
Coronary artery disease, n (%)	3 (2.4)	0	3 (2.7)	0.552
Hypertension, n (%)	43 (34.1)	3 (23.1)	40 (35.4)	0.375
Dyslipidemia, n (%)	30 (23.8)	3 (23.1)	27 (23.9)	0.948
Diabetes mellitus, n (%)	19 (15.1)	2 (15.4)	17 (15.0)	0.974
Smoking, n (%)	91 (72.2)	11 (84.6)	80 (70.8)	0.292
Past chest irradiation, n (%)	36 (28.6)	5 (38.5)	31 (27.4)	0.738
Past anthracycline administration, n (%)	4 (3.2)	0	4 (3.6)	0.491

there are many cases of myocarditis with preserved left ventricular function. Taken together, these findings suggest that there are often subclinical and undiagnosed cases of myocarditis associated with ICI treatment. Therefore, the inclusion of asymptomatic cases of myocarditis in our study was not due to overdiagnosis but rather to pick up silent cases that have been previously ignored. Furthermore, the more remarkable finding of our study is that all of patients with asymptomatic and mild cases could successfully continue ICI treatment with careful clinical follow-up. Currently, the problem that many physicians face in real-world practice is deciding at what point myocarditis should be treated, i.e. when ICI should be discontinued. If ICI-associated myocarditis is suspected, current consensus recommends holding ICIs for any grade of toxicity, including modifications of cardiac biomarkers, and discontinuing ICIs permanently, even for mild toxicity. For most other organ irAEs, it is not recommended to hold ICIs for grade 1 toxicity, but for ICI-associated myocarditis, it is recommended to hold ICIs even for mild grade of toxicity because of the high mortality of this irAE [11]. However, discontinuation of ICI may result in discontinuation of cancer treatment itself, and unnecessary discontinuation should be avoided as much as possible. Our results suggest that ICIs can be continued in cases of mild myocarditis with careful follow-up, which is important for efficient anticancer therapy.

Lastly, we discussed clinical factors that could be useful in screening for myocarditis. Salem et al. [1] reported that ICI combination therapy is the only risk factor for ICI-associated myocarditis. Actually, in our study, no existing cardiovascular risk factors were associated with the occurrence of clinically suspected myocarditis (Table 4). We searched for biomarkers that were expected to have high efficacy due to prospective and frequent assessments. The results reveal that among patients with moderate to severe symptoms, CK elevations (median 22 days; range 7–47 days) preceded troponin-I elevations (median 29.5 days, range 8–48 days). In contrast, CK elevation was not observed in any of the patients with asymptomatic or mild symptoms. Interestingly, several patients developed fatal myocarditis after asymptomatic CK elevation followed by ICI continuation. These findings suggest that CK elevation may occur before myocarditis becomes symptomatic. The report on cross-reactions between myocarditis and myositis in skeletal muscles [12] also supports the possibility that CK elevation may be an early biomarker of severe myocarditis.

The present study provides a comprehensive picture of the incidence and details of ICI-associated myocarditis, which was previously unclear. Although it is not essential to perform all laboratory tests exhaustively, screening with specific biomarkers, such as CK, may be useful for the early detection of myocarditis and prevention of severe disease. Furthermore, even though all patients with moderate to severe myocarditis required discontinuation of ICI treatment, no fatal cases were observed, because screening allowed early intervention. Accordingly, screening using biomarkers is in line with the American Society of Clinical Oncology guidelines [11], which recommend intervention by picking up mild cases and consulting cardiologists.

This study has a limitation that this was a single center study that used only a small number of patients. Thus, this study did not include cases of melanoma or cases in which ICI treatment was combined with ipilimumab treatment because of the reinvestments in Japan. Third, due to the lack of CMR data, a few patients did not exactly meet the diagnostic criteria for clinically suspected myocarditis in the ESC guidelines [3]. Our results, therefore, need to be verified through future studies in larger prospective cohorts.

Conclusions

This study provides insight into the frequency of myocarditis based on a prospective screening of patients treated with ICIs in the real world. The frequency was higher than expected but most cases were of silent or mild and ICI treatment could be continued under careful observation. Additionally, the occurrence of myocarditis was observed at the early stage of ICI treatment. Based on our results, we propose that cardiovascular screening should be performed just after ICI administration. Moreover, our study showed that CK elevation may be a useful, pre-onset screening biomarker for ICI-related myocarditis. Further studies are needed for patient risk stratification and to validate this method of monitoring patients undergoing ICI treatment.

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Data availability

The deidentified participant data will not be shared.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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