Immune checkpoint inhibitors-associated cardiotoxicity in immunotherapy trials on gastrointestinal cancer patients

Yiqun Li1, Yanfeng Wang2, Ning Li3, Xinjun Liang4, Shu Zhang5, Qingxia Fan6, Xianli Yin7, Zhixiang Zhuang8, Yunpeng Liu9, Jingdong Zhang10, Xiaohe Kou1, Haijun Zhong12, Binghe Xu1, Jing Huang1

1Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China; 2Department of Comprehensive Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China; 3Department of Medical Oncology, Henan Cancer Hospital, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, Henan 450008, China; 4Department of Medical Oncology, Hubei Cancer Hospital, Wuhan 430079, China; 5Department of Medical Oncology, Shandong Cancer Hospital, Jinan, Shandong 250117, China; 6Department of Medical Oncology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan 410013, China; 7Department of Medical Oncology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215008, China; 8Department of Medical Oncology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, China; 9Department of Medical Oncology, Liaoning Cancer Hospital, Cancer Hospital of China Medical University, Shenyang, Liaoning 110042, China; 10Department of Medical Oncology, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan 453000, China; 11Department of Medical Oncology, Zhejiang Cancer Hospital, Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, China.

To the Editor: Gastrointestinal (GI) cancer is the most common malignancy in China.1 For many decades, the treatment options for GI cancers have been limited to surgery, radiotherapy, and chemotherapy. Over recent years, immune checkpoint inhibitors (ICIs) that target programmed cell death 1 (PD-1), or its programmed death-ligand 1 (PD-L1), have demonstrated promising efficacies and changed the treatment landscape in GI cancer.2 However, immune-related adverse events (irAEs) can occur during ICI treatment. Furthermore, ICI-associated cardiotoxicity is a rare but potentially fatal toxic effect.

ICI-related cardiotoxicity was initially presented as single case reports at conferences. In 2016, ICI-myocarditis began to be sporadically reported.3 Over recent years, although several small case series, retrospective analyses, and meta-analyses, have emerged, data relating to frequency, clinical features, and outcomes are still limited, especially in the Chinese population.

ICIs have already been approved for use in China by the National Medical Products Administration for patients with GI cancer. We could anticipate that with improved access to ICIs and the expansion of immunotherapy indications, the use of ICI for GI cancer patients will increase dramatically in the coming years, and the life-threatening complication, cardiotoxicity, will necessarily increase as a problem for clinicians. Therefore, there is an urgent need to better characterize ICI-cardiotoxicity in patients with GI cancer. Herein, we reported GI cancer cases who developed ICI-associated cardiotoxicity from six prospective clinical trials (Registration numbers: NCT03704246, NCT02742935, NCT03732508, NCT03099382, NCT03603756, and CTR20191215) conducted between April 19, 2016, and July 13, 2020, at participating centers and compared with patients in the same trials but without cardiotoxicity. Myocarditis was diagnosed according to the clinical diagnostic criteria proposed by Bonaca et al as an operational definition of cancer therapy-associated myocarditis in 2019. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03). The studies were approved by the local research ethics committees, and written informed consent was obtained.

Yiqun Li and Yanfeng Wang contributed equally to this work.

Correspondence to: Jing Huang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China E-Mail: huangjingwe@163.com

Copyright © 2022 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
By the end of July 13, 2020, a total of 291 patients with GI cancer under ICI therapy from the six trials were observed. Nine patients with ICI-associated cardiotoxicity were identified. The baseline demographics of patients with or without cardiotoxicity are summarized in Table 1.

The median age of patients with ICI-cardiotoxicity was 63.5 years and 88.9% (8/9) were males. The most common type of cancer was esophageal cancer. Compared with a non-cardiotoxicity group, a cardiotoxicity group appeared to have a higher prevalence of comorbidities and concomitant medication. Moreover, a significantly higher prevalence of previous mediastinal radiation was observed in patients with esophageal cancer in the cardiotoxicity group (80% (4/5) vs. 27.5% (44/160), P = 0.04). No other factors were identified between the two groups that were predictive of cardiotoxicity.

The overall incidence of ICI-cardiotoxicity was 3.1% (9/291), with an incidence of 3.0% (5/169) in patients receiving anti-PD-1 alone, 3.4% (3/88) in patients receiving a combination of anti-PD-1 and chemotherapy or antiangiogenic therapy, and 4.2% (1/24) in patients receiving anti-PD-L1 combined with chemotherapy. The incidence of cardiotoxicity in patients receiving ICI monotherapy was slightly lower than patients receiving ICI combined with chemotherapy or anti-angiogenic therapy (2.8% (5/179) vs. 3.6% (4/112), P = 0.97).

The clinical features, treatment, and survival of patients with immune-related cardiotoxicity are summarized in Supplementary Table 1, http://links.lww.com/CM9/A981. Electrocardiogram abnormalities presented in seven patients (ST-T changes, n = 3; atrial fibrillation, n = 1; supraventricular tachycardia, n = 1; atrial escape rhythm, n = 1; complete right bundle branch block, n = 1). Two of the three patients with ST-T elevation received both cardiac magnetic resonance (CMR) and coronary angiography (CAG). CMR showed enlargement of both atria in one case but no abnormality was evident in the other case. CAG revealed normal coronary arteries in both patients. The third patient showed a slight ST-T change and did not receive CMR or CAG. The median onset of cardiotoxicity from ICI initiation was 55 days with a non-cardiotoxicity group, a cardiotoxicity group without immune-related cardiotoxicity are summarized in Table 1.

The median time from symptom onset to steroids was 2 days. The mean initial equivalent steroid dose of prednisone was 2.5 mg·kg⁻¹·day⁻¹. The objective response rate was 62.5% (5/8). The median overall survival was 8.9 months (95% confidence interval: 7.3–10.5 months). The median follow-up time was 13.7 months (range 1.2–43.6 months). The median time from an elevation of troponin to decreasing back to normal was 10 days. Five cases permanently discontinued ICIs. Four patients had ICI re-challenged under close monitoring; none of these cases experienced a flare of cardiotoxicity.

Here we report, to the best of our knowledge, the first analysis of ICI-associated cardiotoxicity in GI cancer patients in which the cases were all derived from prospectively registered immunotherapy trials in China. Our analyses showed that ICI-associated cardiotoxicity occurred very early after therapy initiation and was more commonly seen in patients with comorbidities and receiving ICIs combined with chemotherapy or target therapy. Previous mediastinal radiation was associated with a higher risk of cardiotoxicity in patients with esophageal cancer. The most common concurrent irAEs was myositis. Most patients received steroids and 77.8% recovered from cardiac events.

Table 1: Baseline demographics of GI cancer patients with and without immune-related cardiotoxicity.

| Demographics                             | Total (n = 291) | Cardiotoxicity (n = 9) | Without cardiotoxicity (n = 282) |
|-----------------------------------------|-----------------|------------------------|----------------------------------|
| Age at start of ICI (years)             | 59 (38–74)      | 64 (44–66)             | 59 (38–74)                       |
| Sex                                      |                 |                        |                                  |
| Male                                     | 229 (78.7)      | 88 (88.9)              | 221 (78.4)                       |
| Female                                   | 62 (21.3)       | 1 (11.1)               | 61 (21.6)                        |
| Comorbidities                            |                 |                        |                                  |
| Hypertension                             | 58 (19.9)       | 1 (11.1)               | 57 (20.2)                        |
| Current or prior smoking                 | 144 (49.5)      | 5 (55.6)               | 139 (49.3)                       |
| Body mass index (kg/m²)                  | 22.0 ± 3.7      | 21.1 ± 4.1             | 21.9 ± 3.6                       |
| Tumor types                              |                 |                        |                                  |
| Esophageal cancer or esophagogastric     | 165 (56.7)      | 5 (55.6)               | 160 (56.7)                       |
| junction cancer                          |                 |                        |                                  |
| Gastric cancer                           | 63 (21.6)       | 2 (22.2)               | 61 (21.6)                        |
| Colorectal cancer                        | 56 (19.2)       | 1 (11.1)               | 55 (19.3)                        |
| Hepatobiliary cancer                     | 5 (1.7)         | 1 (11.1)               | 4 (1.4)                          |
| Pancreatic cancer                        | 1 (0.3)         | 0                      | 1 (0.4)                          |
| Anul cancer                              | 1 (0.3)         | 0                      | 1 (0.4)                          |
| Prior chemotherapy or radiation          |                 |                        |                                  |
| Anthracyclines                           | 14 (4.8)        | 1 (11.1)               | 13 (4.6)                         |
| Herceptin                                | 45 (15.5)       | 1 (11.1)               | 44 (15.6)                        |
| VEGF inhibitors                          | 48 (16.5)       | 4 (44.4)               | 44 (15.6)                        |
| Mediastinal radiation                    |                 |                        |                                  |
| Concomitant medication                   |                 |                        |                                  |
| ACEI, ARB, or CCB                        | 40 (13.7)       | 3 (33.3)               | 37 (13.1)                        |
| Aspirin                                  | 7 (2.4)         | 0                      | 7 (2.5)                          |
| Hypoglycemic agents                      | 15 (5.2)        | 2 (22.2)               | 13 (4.6)                         |
| ICI-treatment strategies                 |                 |                        |                                  |
| Anti-PD-1 + chemotheraphy                | 169 (58.1)      | 5 (55.6)               | 164 (58.2)                       |
| Anti-PD-1 + chemotherapy + target therapy | 38 (13.2)     | 2 (22.2)               | 36 (12.8)                        |
| Anti-PD-L1 + chemotherapy                | 30 (10.3)       | 1 (11.1)               | 29 (10.3)                        |
| Anti-PD-L1 + chemotherapy + target therapy| 10 (3.4)       | 0                      | 10 (3.5)                         |
| Anti-PD-L1 + chemotherapy                | 24 (8.2)        | 1 (11.1)               | 23 (8.2)                         |
| ICI monotherapy                          | 179 (61.5)      | 5 (55.6)               | 174 (61.7)                       |
| ICI + other therapies                    | 112 (38.5)      | 4 (44.4)               | 108 (38.3)                       |

Data were presented by n (%), median (range), or mean ± SD. All P > 0.05 between the cardiotoxicity group and non-cardiotoxicity group. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium-channel blocker; COPD: Chronic obstructive pulmonary disease; GI: Gastrointestinal; ICIs: Immune checkpoint inhibitors; PD-1: Programmed death 1; PD-L1: Programmed death-ligand 1; VEGF: Vascular endothelial growth factor.
The true incidence of ICI-cardiotoxicity currently remains unknown. Previous studies focused mainly on the rates of ICI-myocarditis, ranging from 0.09% to 1.14%. We observed an incidence rate of 3.1% for ICI-cardiotoxicity. The reason for the higher rates reported in our study might be due to the inclusion of cases with cardiovascular events beyond myocarditis and the closer monitoring of patients as part of clinical trials. Moreover, due to the ambiguous description of cardiac irAEs in the CTCAE, and the difficulty in diagnosing myocarditis, the incidence of cardiac irAEs is likely to have been underestimated.

We observed a higher number of esophageal cancer patients in both the entire cohort and the ICI-cardiotoxicity group. Of note, four of the five esophageal cancer cases with cardiotoxicity received mediastinal radiation previously. Traditionally, in studies of breast cancer or Hodgkin’s lymphoma, cardiotoxicity has been viewed as a late side effect of radiation therapy. However, in a recent study focusing on esophageal cancer patients, high-grade cardiac events were found to be common and occurred within 2 years, at a median onset of 7 months after radiation. Radiation alone can cause heart injury by inducing or accelerating various physiological changes, including endothelial dysfunction, inflammation, and cardiac fibrosis. PD-L1 was found to be enriched in cardiomyocytes and the endothelium to help regulate self-tolerance, and cardiomyopathy mediated by autoreactivity developed in PD-1-deficient mice. Moreover, patients with a history of autoimmune disease appear to be predisposed to radiation toxicities. Du et al. previously showed that a combination of PD-1 blockade and radiation increased the cardiac toxicity caused by cardiac radiation via CD8+ T cell-mediated myocarditis with associated fibrosis. Therefore, due to the relatively early onset of radiation-induced cardiotoxicity and the potential synergistic effect of PD-1 blockade and radiation, esophageal cancer patients who received prior mediastinal radiation might be more susceptible to ICI-induced cardiac inflammation. However, given the limited sample size involved in this study, more evidence is needed to draw further conclusions. However, in clinical practice, it would be reasonable to suggest that closer monitoring of cardiovascular events should be taken while giving ICIs to esophageal cancer patients who received mediastinal radiation previously, especially in those within 2 years of radiation. In the current study, the time from mediastinal radiation to ICI-cardiotoxicity was 6.0, 10.6, 13.9, and 29.7 months in the four patients, respectively.

Our study focused on ICI-related cardiotoxicity extending beyond myocarditis and therefore, took a very different approach than previous studies. While myocarditis was the major presentation of ICI-cardiotoxicity reported from clinical trials, other forms of ICI-cardiotoxicity, such as pericarditis, atrioventricular conduction disease, and arrhythmias, have also been reported and sometimes overlooked by the treating physicians. New-onset arrhythmias that cannot be explained by any other diagnosis should raise the concern of ICI-cardiotoxicity and additional diagnostic information might be needed. In the future, a deeper understanding of the molecular mechanisms involved in ICI-associated cardiotoxicity will be needed as this could help us to identify new biomarkers, determine new treatment strategies, and improve the management of these patients.

To conclude, cardiotoxicity associated with ICI therapy in patients with GI cancer is uncommon but fatal. Previous mediastinal radiation in patients with esophageal cancer might be associated with an increased risk of ICI-cardiotoxicity. Early identification and the optimization of treatment for myocarditis should be an important focus of future studies. This potentially lethal side effect requires clinical vigilance and a novel therapeutic approach to minimize its life-threatening toxicity.

References

1. Zheng RS, Sun KX, Zhang SW, Zeng HM, Zou XN, Chen R, et al. Report of cancer epidemiology in China, 2015 (in Chinese). Chin J Oncol 2019;41:19–28. doi: 10.3760/cma.j.issn.0253-3766.2019.01.005.

2. Huang J, Xu J, Chen Y, Zhuang W, Zhang Y, Chen Z, et al. Camrelizumab versus investigator’s choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol 2020;21:832–842. doi: 10.1016/S1470-2045(20)30110-8.

3. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375:1749–1753. doi: 10.1056/NEJMoa1609214.

4. Bonaca MP, Olenchock BA, Salem JE, Wittuvot SD, Ederby S, Cohen A, et al. Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. Circulation 2019;140:80–91. doi: 10.1161/CIRCULATIONAHA.118.034497.

5. Mahmoud SS, Bradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 2018;71:1755–1764. doi: 10.1016/j.jacc.2018.02.037.

6. Wang F, Qin S, Lou F, Chen FX, Shi M, Liang X, et al. Retrospective analysis of immune checkpoint inhibitor-associated myocardiitis from 12 cancer centers in China. J Clin Oncol 2020;38:e15130. doi: 10.1200/JCO.2020.38.15_suppl.e15130.

7. Wang X, Palaskas NL, Yusef SW, Abe JI, Lopez-Mattei J, Bansch J, et al. Incidence and onset of severe cardiac events after radiotherapy for esophageal cancer. J Thorac Oncol 2020;15:1682–1690. doi: 10.1016/j.jtho.2020.06.014.

8. Du S, Zhou L, Alexander GS, Park K, Yang L, Wang N, et al. PD-1 modulates radiation-induced cardiac toxicity through cytotoxic T lymphocytes. J Thorac Oncol 2018;13:510–520. doi: 10.1016/j.jtho.2017.12.002.

How to cite this article: Li Y, Wang Y, Li N, Liang X, Zhang S, Fan Q, Yin X, Zhuang Z, Liu Y, Zhang J, Kou X, Zhong H, Xu B, Huang J. Immune checkpoint inhibitors-associated cardiotoxicity in immunotherapy trials on gastrointestinal cancer patients. Chin Med J 2022;135:988–990. doi: 10.1097/CM9.0000000000002054