Appendix 1

Diagnosis criteria of immune checkpoint inhibitor-associated myocarditis

Immune checkpoint inhibitor (ICI)-associated myocarditis was diagnosed based on Chinese expert consensus on the surveillance and management of immune checkpoint inhibitor-related myocarditis (2020 version) (1). Diagnosis criteria were as followed:

Definite myocarditis: any of the following:

1. Tissue pathology diagnostic of myocarditis (e.g., on biopsy or autopsy)
2. Cardiac magnetic resonance imaging (CMR) diagnostic of myocarditis, a clinical syndrome, and one of following:
   a. Elevated biomarker of cardiac myonecrosis
   b. Electrocardiographic (ECG) evidence of myo-pericarditis
3. New wall motion abnormality (WMA) on echocardiogram not explained by another diagnosis (e.g. acute coronary syndrome ruled out by angiography, trauma, stress induced cardiomyopathy, sepsis) and all of the following:
   a. Clinical syndrome consistent with myocarditis
   b. Elevated biomarker of cardiac myonecrosis
   c. ECG evidence of myo-pericarditis
   d. Negative angiography or other testing to exclude obstructive coronary disease

Probable myocarditis: any of the scenarios below that are not explained by another diagnosis (e.g., acute coronary syndrome, trauma, stress induced cardiomyopathy)

1. CMR with findings diagnostic of myocarditis without any of the following (when screening CMR is being performed routinely as in the context of trial procedure)
   a. Clinical syndrome consistent with myocarditis
   b. Elevated biomarker of cardiac myonecrosis
   c. ECG evidence of myo-pericarditis
2. Non-specific CMR findings suggestive of myocarditis with any 1 or more of the following:
   a. Clinical syndrome consistent with myocarditis
   b. Elevated biomarker of cardiac myonecrosis
   c. ECG evidence of myo-pericarditis
3. New WMA on echocardiogram with a clinical syndrome consistent with myocarditis and either:
   a. Elevated biomarker of cardiac myonecrosis
   b. ECG evidence of myo-pericarditis
4. A scenario meeting criteria for possible myocarditis (see below) with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging showing patchy cardiac FDG uptake without another explanation

Possible myocarditis: any of the scenarios below that are not explained by another diagnosis (e.g., acute coronary syndrome, trauma, stress induced cardiomyopathy)

1. Non-specific CMR findings suggestive of myocarditis with none of the following:
   a. Clinical syndrome consistent with myocarditis
   b. Elevated biomarker of cardiac myonecrosis
   c. ECG evidence of myo-pericarditis
2. New WMA on echocardiogram and 1 of the following:
   a. Clinical syndrome consistent with myocarditis
   b. ECG evidence of myo-pericarditis
3. New elevated biomarker (beyond baseline) and 1 of the following:
   a. Clinical syndrome consistent with myocarditis
   b. ECG evidence of myo-pericarditis

Subclinical myocardial injury

1. Only cardiac injury biomarkers were elevated (excluding other diseases)
2. Without clinical symptoms, electrocardiogram, echocardiogram, or CMR changes

Treatment criteria of immune checkpoint inhibitor-associated myocarditis

Treatment strategy for immune checkpoint inhibitor (ICI)-associated myocarditis was based on the Chinese expert consensus on the surveillance and management of immune checkpoint inhibitor-related myocarditis (2020 version) (32). Treatment details are as follows:

1. General treatment
   - Discontinue ICI immediately
   - Consult with a cardiovascular physician or critical care physician if necessary
   - Attention should be paid to concurrent immunotoxicity of other organs, and multidisciplinary diagnosis and treatment teams should be formed if necessary.
   - Electrocardiographic (ECG), blood pressure, and oxygenation monitoring should be performed in patients with arrhythmia and unstable hemodynamics. Patients with heart failure should be managed according to heart failure guidelines.
2. Administration of steroids
   - For unstable subclinical myocardial damage (progressive elevation of cardiac troponin), oral

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prednisone (1–2 mg/kg/day) is recommended, and the dose should be reduced after 5 to 7 days. The first dose reduction is 25% to 40%, and then the dose is reduced once a week. The reduction process should not be shorter than 4 weeks.

- For mild myocarditis, intravenous methylprednisolone (1–2 mg/kg/day) or equivalent (4 mg methylprednisolone =5 mg prednisone) oral prednisone 5–7 days depending on the situation is recommended. After the improvement of the condition, the dose could be reduced once every 1 to 2 weeks. The reduction process should not be shorter than 4–6 weeks.
- For severe and critical myocarditis, intravenous methylprednisolone (1 g/day) is recommended for 3 to 5 days. After the improvement of the condition, the dose of methylprednisolone could be changed to 1 to 2 mg/kg/day. After the recovery of conduction block and cardiac function, the dose could be reduced once every 1 to 2 weeks. The reduction process should not be shorter than 6–8 weeks.
- Steroids should be the first-line and critical treatment for ICI-associated myocarditis
- If myocarditis aggravates in the process of steroids reduction, up-dose steroids or combination of mycophenolate mofetil (MMF), tacrolimus, infliximab, and other agents are should be selected as appropriate.

3. Further interventions
    - If no improvement within 24–48 hours on steroids, further interventions should be considered.
    - The dose of intravenous immunoglobulin is 2 g/kg (20–40 g/d for the first 2 days, and then 10–20 g/d for 5 to 7 days).
    - Plasmapheresis and lymphocyte clearance suppress humoral and cellular immunity by removing cytokines, immune complexes, and activated lymphocytes from plasma.
    - When available, critical myocarditis is recommended for referral to the cardiovascular ward or intensive care unit with respiratory and circulatory support.

References

32. Society of Integrative Cardio-Oncology China Anti-Cancer Association, The Cardio-Oncology Group of the Chinese Society of Cardiovascular Diseases of Chinese Medical Association, Chinese College of Cardiovascular Physicians Specialized Committee on Cardio-Oncology Chinese Medical Doctor Association, et al. Chinese expert consensus on the surveillance and management of immune checkpoint inhibitor-related myocarditis (2020 version). Chinese Journal of Clinical Oncology 2020;47:1027-38.

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Table S1 Patient case summary for ICI-related myocarditis patients

Patient	Gender	Categories of myocarditis[†]	Checkpoint inhibitor	Number of ICI doses when myocarditis onset	Time to myocarditis onset from ICI initiation	Symptoms and signs	Imaging characteristics	Other side effects	Time to initiation of steroids from symptom onset[‡]	Treatment	Treatment outcome
1	M	Probable	Pembrolizumab	1	12 days	Fatigue, myalgia, blurred vision, edema, orthopnea, shortness of breath, chest tightness	ECG, TTE, CXR: abnormal CAG: normal	Myositis, pneumonia, neuritis, skin rash	13 days	First line: intravenous methylprednisolone 80 mg daily until clinically stable, followed by 40 mg daily, then gradually decreased, second line: combined use with intravenous immunoglobulin 10–20 mg	Myocarditis resolved
2	F	Possible	Pembrolizumab	1	43 days	Fatigue, edema	ECG, TTE: abnormal CXR: normal	Myositis, encephalitis	1 day	Discharged after an intravenous methylprednisolone 80 mg	Myocarditis resolved
3	M	Probable	Pembrolizumab	1	10 days	Shortness of breath, chest pain	ECG, TTE, CAG: abnormal CXR: normal	None	1 day	Discharged after intravenous methylprednisolone 240–330 mg/d for 2 days, combined use with intravenous immunoglobulin 10 mg daily	Lost to follow-up after self-discharge before remission
4	M	Possible	Sintilimab	1	21 days	Blurred vision, shortness of breath, chest tightness	ECG, TTE, CAG: abnormal CXR: normal	None	1 day	Discharged after intravenous methylprednisolone 1,000 mg/d for two days, combined use with intravenous immunoglobulin 10 mg daily	Death after self-discharge before remission
5	M	Definite	Sintilimab	1	48 days		ECG, TTE, CMR: abnormal CXR: normal	Myositis	1 day	First line: intravenous methylprednisolone 1,000 mg/d for 3 days, followed by 500 mg/d, then gradually decreased, second line: combined use with intravenous immunoglobulin 10 mg	Myocarditis resolved
6	F	Definite	Pembrolizumab	5	207 days	Edema, orthopnea, shortness of breath, chest tightness, chest pain, palpitation	ECG, TTE, CMR, CXR: abnormal	None	2 days	First line: intravenous methylprednisolone 1,000 mg/d for 3 days, followed by 250 mg/d, then gradually decreased, second line: combined use with intravenous immunoglobulin 15 mg	Myocarditis resolved
7	M	Possible	Toripalimab	1	1 day	Fatigue, shortness of breath, chest tightness	ECG, TTE, CXR: abnormal	None	Immediately	Discharged after intravenous methylprednisolone 1,000 mg/d for 3 days	Myocarditis resolved
8	F	Possible	Pembrolizumab	1	6 days	Shortness of breath, chest tightness	ECG, TTE, CXR: abnormal	Pneumonia, hypothyroidism	–	Discharged after intravenous methylprednisolone 1,000 mg/d for 3 days	Myocarditis resolved
9	M	Definite	Pembrolizumab	1	23 days	Fatigue, myalgia, edema, shortness of breath, chest tightness, chest pain, palpitation	ECG, TTE, CMR, CXR, EMB, CAG: abnormal	Myositis, pneumonia, encephalitis, neuritis	3 days	First line: intravenous methylprednisolone 580–500 mg/d for 4 days, followed by 160 mg daily, then gradually decreased, second line: combined use with intravenous immunoglobulin 10 mg	Myocarditis resolved
10	M	Possible	Camrelizumab	6	133 days	Fatigue, myalgia, edema, chest pain	ECG, CAG: abnormal CMR, TTE, CXR: normal	Myositis	1 day	Once intravenous methylprednisolone 80 mg, followed by 32 mg daily, then gradually decreased	Myocarditis resolved
11	M	Probable	Sintilimab	6	185 days	Myalgia	ECG, TTE: abnormal CXR: normal	Myositis, pneumonia, neuritis, skin rash, hypothyroidism	2 days	First line: intravenous methylprednisolone 120 mg daily until clinically stable, followed by 80 mg daily, then gradually decreased	Myocarditis resolved
12	M	Probable	Sintilimab	1	25 days	Fatigue, myalgia, orthopnea, shortness of breath, chest tightness	ECG, TTE: abnormal CXR: normal	Myositis, neuritis	Immediately	First line: intravenous methylprednisolone 500 mg/d for 2 days, followed by 250 mg daily, continue to use 500 mg when condition worsened, then gradually decreased, second line: combined use with intravenous immunoglobulin 10 mg	Myocarditis resolved
13	F	Probable	Sintilimab + tislelizumab	7	266 days	Myalgia, shortness of breath, chest tightness, chest pain, palpitation	ECG, TTE: abnormal CXR: normal	None	Immediately	First line: intravenous methylprednisolone 250 mg/d for 3 days, followed by 80 mg daily, then gradually decreased, second line: combined use with intravenous immunoglobulin 5 mg	Myocarditis resolved
14	M	Probable	Tislelizumab	1	45 days	Fatigue, palpitation	ECG, TTE: abnormal CXR: normal	Myositis, neuritis	54 days	First line: intravenous methylprednisolone 500 mg daily until clinically stable, then gradually decreased, second line: combined use with intravenous immunoglobulin 5 mg	Myocarditis resolved

[†], according to the ASCO guidelines (9); [‡], 13 of the 14 myocarditis patients had this information. ICI, immune checkpoint inhibitors; ECG, electrocardiogram; TTE, transthoracic echocardiography; CXR, chest X-ray; CAG, coronary arteriography; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy.

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