



Immunotherapy

Immunotherapy

Taylor & Francis
Taylor & Francis Group

ISSN: 1750-743X (Print) 1750-7448 (Online) Journal homepage: www.tandfonline.com/journals/iimy20

Fatal Toxicity Induced by anti-PD-1 Immune Checkpoint Inhibitor in Thymic Epithelial Tumor

Xuquan Jing, Hui Zhu, Yuying Li, Wenxiao Jia, Xiaoyang Zhai, Ji Li & Jinming Yu

To cite this article: Xuquan Jing, Hui Zhu, Yuying Li, Wenxiao Jia, Xiaoyang Zhai, Ji Li & Jinming Yu (2022) Fatal Toxicity Induced by anti-PD-1 Immune Checkpoint Inhibitor in Thymic Epithelial Tumor, *Immunotherapy*, 14:14, 1097-1107, DOI: [10.2217/imt-2021-0215](https://doi.org/10.2217/imt-2021-0215)

To link to this article: <https://doi.org/10.2217/imt-2021-0215>



Published online: 12 Sep 2022.



Submit your article to this journal



Article views: 250



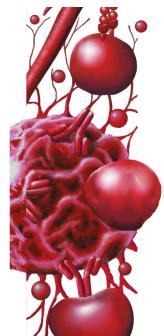
View related articles



View Crossmark data



Citing articles: 4 View citing articles



Fatal toxicity induced by anti-PD-1 immune checkpoint inhibitor in thymic epithelial tumor

Xuquan Jing^{1,2}, Hui Zhu^{1,2}, Yuying Li^{1,2}, Wenxiao Jia^{1,2}, Xiaoyang Zhai^{1,2}, Ji Li^{1,2} & Jinming Yu^{*,1,2}

¹Department of Radiation Oncology, Shandong Cancer Hospital & Institute, Shandong University Cancer Center, Shandong University, Jinan, Shandong, 250117, China

²Department of Radiation Oncology, Shandong Cancer Hospital & Institute Affiliated to Shandong First Medical University, Shandong Academy of Medical Sciences, Jinan, Shandong, 250117, China

*Author for correspondence: sdyujinming@163.com

A standard treatment for advanced thymic epithelial tumors (TETs) after initial treatment remains unavailable to date. Targeted immune checkpoint inhibitors (ICIs) of the programmed cell death-1 (PD-1) pathway may produce objective responses in TETs, notably thymic carcinoma. Findings of clinical trials suggested ICIs are a practical choice. However, the risk of severe immuno-related adverse events is higher in TETs. Concerning histologic subtypes, thymomas are more frequently associated with autoimmune disorders than carcinomas, so close monitoring is needed for thymomas. In this article, we describe four cases of fatal toxicity caused by anti-PD-1 therapy in TETs. Four patients with metastatic thymomas or carcinoma difficult to treat with first-line standard chemotherapy were treated with the anti-PD-1 drug pembrolizumab or sintilimab. The association of PD-1 inhibitors with a high proportion of severe immuno-related adverse events in TETs necessitates attentive monitoring during treatment.

Plain language summary: Thymic epithelial tumors are the most common malignancy of the anterior mediastinum in adults, with the occurrence of approximately 1.5 cases/million. Surgery is usually the treatment of choice. However, treatment options for advanced disease are poorly understood, and data are limited. Several studies have assessed the objective responses of immune checkpoint inhibitors in patients with advanced thymic epithelial tumors. Anti-cancer immunity also increases the risk of developing adverse events related to immunotherapy. Some patients can experience lethal toxicity. This article presents four cases of developing severe adverse events to exercise caution in prescribing these agents for thymic epithelial tumor, in particular thymoma.

First draft submitted: 5 August 2021; Accepted for publication: 22 June 2022; Published online: 12 September 2022

Keywords: case report • fatal toxicities • immune check point inhibitor • programmed cell death-1 • thymic epithelial tumor

Thymic epithelial tumors (TETs) are common malignant tumors of the anterior mediastinum in adults [1,2]. The histological classification of TETs is based on the incidence of non-malignant thymic epithelial cells and the lymphocyte ratio. According to the 2015 classification by the World Health Organization (WHO), TETs can be divided into types A, AB, B1, B2, B3 and thymic carcinoma [3]. The treatment of TETs requires a multidisciplinary approach. If the disease is localized, surgical intervention is the only radical treatment option. Adjuvant radiotherapy (RT) has been widely applied in advanced stages of the disease when the surrounding tissues present evidence of tumor invasion or postoperative R1 and R2 residual tumor. At present, platinum-based systemic chemotherapy is the treatment standard for metastatic or non-surgical refractory/recurrent disease, but a standard treatment after the failure of first-line treatment is lacking [4]. For this setting, alternative options include immunotherapeutic modalities, such as treatment with immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1) receptor or its ligand PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [5].

Table 1. Studies and incidence of immuno-related adverse events and histology from literature review.

Immune-related adverse event	NCT02364076 (Pembrolizumab)	NCT02607631 (Pembrolizumab)		Japanese study (Nivolumab)	NCT01772004 (Avelumab)
Histology	Thymic carcinoma	Thymomas	Thymic carcinoma	Thymic carcinoma	Thymoma
Number of patients	40	7	26	15	7
Immuno-related adverse events, n [%]					
Myasthenia gravis	1 [3]	1 [14]	2 [8]	0 [0]	0 [0]
Myocarditis	2 [5]	3 [43]	0 [0]	0 [0]	4 [57]
Polymyositis	3 [8]	0 [0]	0 [0]	0 [0]	4 [57]
Hepatitis	2 [13]	2 [29]	2 [8]	0 [0]	4 [57]
Pancreatitis	1 [3]	0 [0]	0 [0]	0 [0]	0 [0]
Bullous pemphigoid	1 [3]	0 [0]	0 [0]	0 [0]	0 [0]
Thyroiditis	0 [0]	1 [14]	1 [4]	0 [0]	0 [0]
Colitis	0 [0]	1 [14]	0 [0]	0 [0]	0 [0]
Nephritis	0 [0]	1 [14]	0 [0]	0 [0]	0 [0]
Conjunctivitis	0 [0]	1 [14]	0 [0]	0 [0]	0 [0]
Subacute myoclonus	0 [0]	0 [0]	1 [4]	0 [0]	0 [0]
Enteritis	0 [0]	0 [0]	0 [0]	0 [0]	1 [14]
Cranial neuropathy	0 [0]	0 [0]	0 [0]	0 [0]	1 [14]
Type 1 diabetes mellitus	1 [3]	0 [0]	0 [0]	0 [0]	0 [0]
Dermatitis	0 [0]	2 [29]	0 [0]	0 [0]	0 [0]
AST increase	0 [0]	0 [0]	0 [0]	1 [6]	0 [0]
Adrenal insufficiency	0 [0]	0 [0]	0 [0]	1 [6]	0 [0]

Several phase I/II clinical trials have evaluated the potential efficacy of PD-1 inhibitors in the treatment of thymic tumors. These studies have indicated that ICIs can occasionally produce objective responses to TETs in the clinical setting [6–8]. Activating anticaner immunity also increases the risk of immune-related adverse events (irAEs) [9]. Most irAEs observed in non-TET patients belong to low-to-moderate grade and can be controlled by an established treatment plan [10,11]. Published trials have reported that 15–62.5% of patients with TETs developed irAEs (Table 1). The percentage of grade 3 or higher irAEs in TETS is significantly higher than that in other epithelial tumors, such as non-small-cell lung cancer (NSCLC) [12], and some patients have experienced life-threatening toxicities.

In this paper, we report four cases of metastatic TETs refractory to platinum-based chemotherapy, subsequently treated with anti-PD1 agents, and experienced fatal irAEs.

Case descriptions

Case 1

A 56-year-old Chinese man was admitted to our hospital in April 2017 with bilateral upper limb weakness. Chest computed tomography (CT) scan revealed a mass located at the anterior mediastinum. A median sternotomy for a radical thymectomy was performed, and the pathological diagnosis was WHO type B1 thymoma (Figure 1A), with the tumor invading the pericardium and left upper pulmonary lobe. Subsequently, three cycles of cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy were administered. The patient refused any additional chemotherapy and received regular follow-up. Positron emission computed tomography-CT in August 2018 revealed metastasis of the pleura and left diaphragmatic angle (Figure 1B). Subsequently, the patient received five cycles of second-line chemotherapy with liposome-encapsulated paclitaxel and carboplatin. The patient achieved a partial response (PR) and stable disease (SD) after two and four courses, respectively, in accordance with the modified Response Evaluation Criteria in Solid Tumors. Four months later (May 2019), a CT scan revealed that the mass in the left diaphragmatic angle was enlarged (Figure 1C). After discussion with the multidisciplinary clinical team, RT to treat the left diaphragmatic angle mass and treatment with the anti-PD1 inhibitor sintilimab (Tvyt®, Innovent Medicine, Suzhou, China) were conducted. 5 days after the first injection of sintilimab, the patient presented fever and chest tightness. Electrocardiogram (ECG) examination suggested that this patient experienced third-degree atrioventricular block (Figure 1D). After 4 days, the patient was administered with atropine

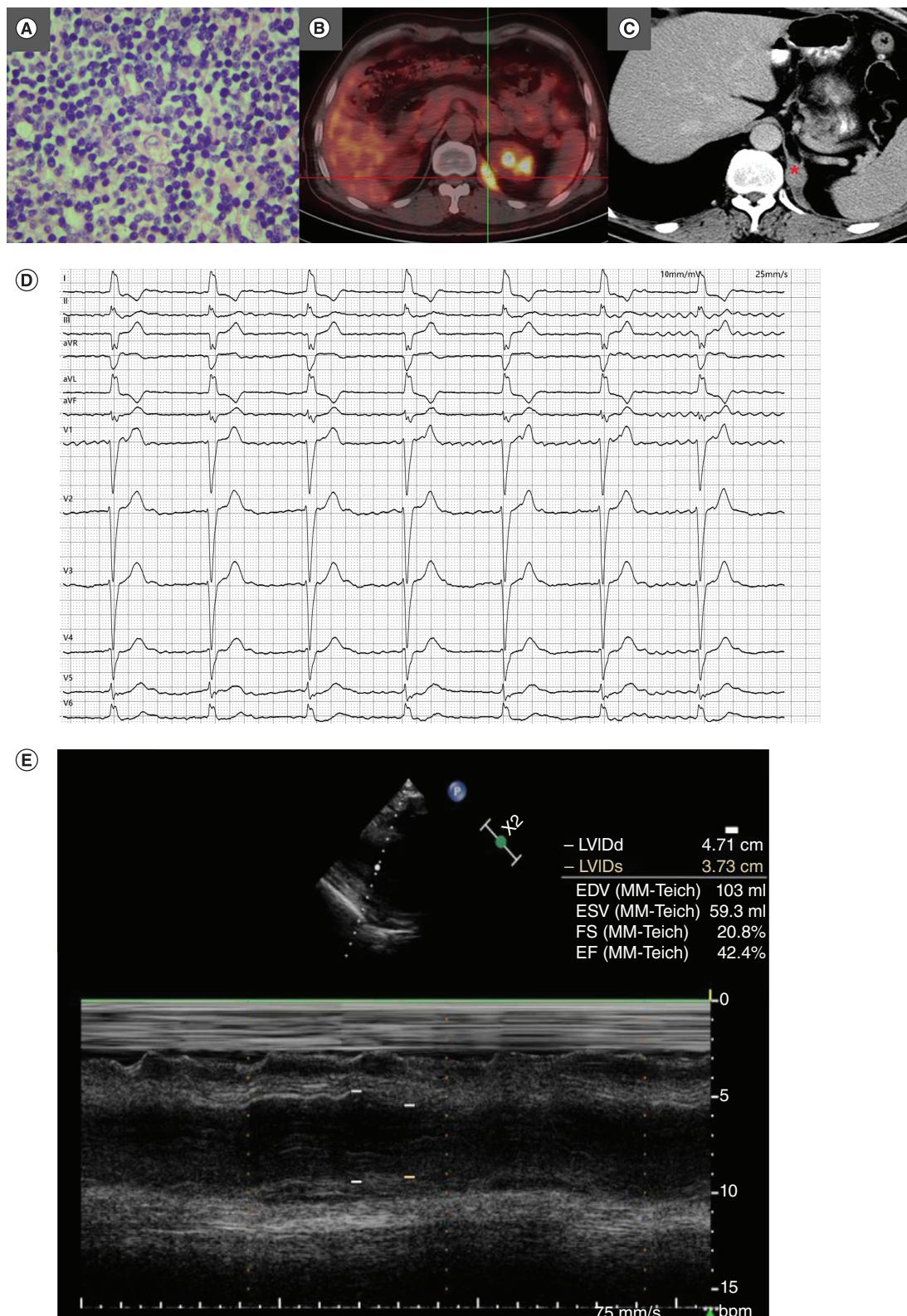


Figure 1. Characteristic of patient 1. (A) Pathological diagnosis of case 1 was WHO type B1 thymoma. (B) Metastasis of pleura and left diaphragmatic angle. (C) Enlarged mass in left diaphragmatic angle. (D) Echocardiogram examination suggested third-degree atrioventricular block. (E) Echocardiogram showed acute heart failure with a left ventricular ejection fraction less than 50%.

and inotropic agents, followed by 2 mg/kg prednisolone. An echocardiogram showed acute heart failure with a left ventricular ejection fraction less than 50% (Figure 1E), and the patient died 3 days following admission to the cardiology intensive care unit (CICU).

Case 2

A 46-year-old woman was diagnosed with metastatic B1 thymoma in accordance with the WHO classification since 2011. She had no history of autoimmunity. She was resistant to three previous lines of therapy. In June 2018, CT scan revealed multiple pleural and diaphragmatic metastases (Figure 2A). Histological evaluation confirmed the diagnosis of B1 thymoma (Figure 2B). Her tumor was positive for microsatellite stability and showed negative PD-L1 expression on the surface of cancer cells (Figure 2C). The tumor mutation burden (TMB) was determined to be 0.8 mutations/Mb. A multidisciplinary antitumor strategy consist of radiotherapy (metastatic tumors: DT 54Gy/18f). Because of failure of former three lines treatment, strong willingness of patient and lack of standard treatment for later line, checkpoint inhibitor (sintilimab) was attempted after multidisciplinary discussion. 10 days after the first sintilimab administration, the patient presented fever and fatigue. A CT scan revealed reduced metastatic tumors and no signs of infection. The patient presented increased transaminase levels and myocardial enzyme (troponin and pro-BNP) markers. Her ECG showed third-degree atrioventricular block (Figure 2D) with no dynamic changes. Thus, she was transferred to the CICU and received corticosteroids and antiarrhythmics for acute autoimmune myocarditis caused by sintilimab. Despite aggressive treatment interventions, the patient still suffered decompensated heart failure and ventricular arrhythmia (Figure 2E). The patient died 10 days after admission to the CICU.

Case 3

A 62-year-old woman presented with a mass in suprasternal fossa. A median sternotomy for a radical thymectomy was performed, and pathological diagnosis revealed a thymic carcinoma in accordance with the WHO classification (Figure 3A). Given evidence of the tumor invading into the surrounding striated muscle, adjuvant radiation (62 Gy) and six cycles of CAP chemotherapy were performed postoperatively. A routine follow-up CT scan in Dec. 2018, approximately 2 months after the last round of chemotherapy, revealed that the tumor recurred with metastases to the bilateral lung, lymph nodes, and bones. Given the unresectable disease, the patient was administered three cycles of chemotherapy consisting of carboplatin and paclitaxel liposome from December 2018 to March 2019. The patient refused further chemotherapy and remained with SD for 6 months. A follow-up CT scan in September 2019 showed significant disease progression (Figure 3B), and the patient was transferred to our hospital. Repeat biopsy of the lung mass showed thymic carcinoma, and PD-L1 staining indicated that PD-L1 expression was less than 1% (Figure 3C). After consultation with the multidisciplinary clinical team, anlotinib was administered for 2 months; however, this treatment was discontinued 1 month after administration because of severe oral ulceration. Subsequently, the patient received RT (52 Gy/26 f) for thymic tumor. A follow-up CT scan 2 months after RT revealed SD. Thus, treatment with the anti-PD-1 inhibitor sintilimab was conducted. 6 days later after the first injection of sintilimab, the patient presented chest tightness. Ultrasonographic scan showed massive pericardiac fluid (Figure 3D). She was administered with 2 mg/kg prednisolone. The patient refused further treatment because of the general deterioration of her conditions. The patient died 5 days after hospital discharge.

Case 4

A 77-year-old Chinese woman was admitted to our hospital in July 2019 with dyspnea that worsened with activity. A CT scan revealed a mediastinal mass and pleural effusion. PET-CT showed moderate ¹⁸F-fluorodeoxyglucose uptake in the mediastinal mass (Figure 4A). The anterior mediastinal tumor was classified as type AB (Figure 4B) thymoma in accordance with the WHO classification after percutaneous needle biopsy. Histological evaluation showed the presence of stage IV malignant thymus tumor. The status of PD-L1 was less than 1% (Figure 4C). Thus, the patient was initially treated with a two-cycle combination regimen consisting of cisplatin and paclitaxel liposome accompanied by thoracic drainage and perfusion with bevacizumab. A follow-up CT scan following two cycles of first-line chemotherapy revealed SD. She was very resistant to chemotherapy because of fatigue and nausea but had a strong willingness for pembrolizumab. After discussion with the multidisciplinary clinical team, the patient received chest RT and pembrolizumab. Ten days later, she developed acute chest pain and hypotension. She presented increased transaminase levels and myocardial enzyme (troponin and pro-BNP) markers. The patient died during emergency transfer to the hospital. The emergency medication on the ambulance was not recorded.

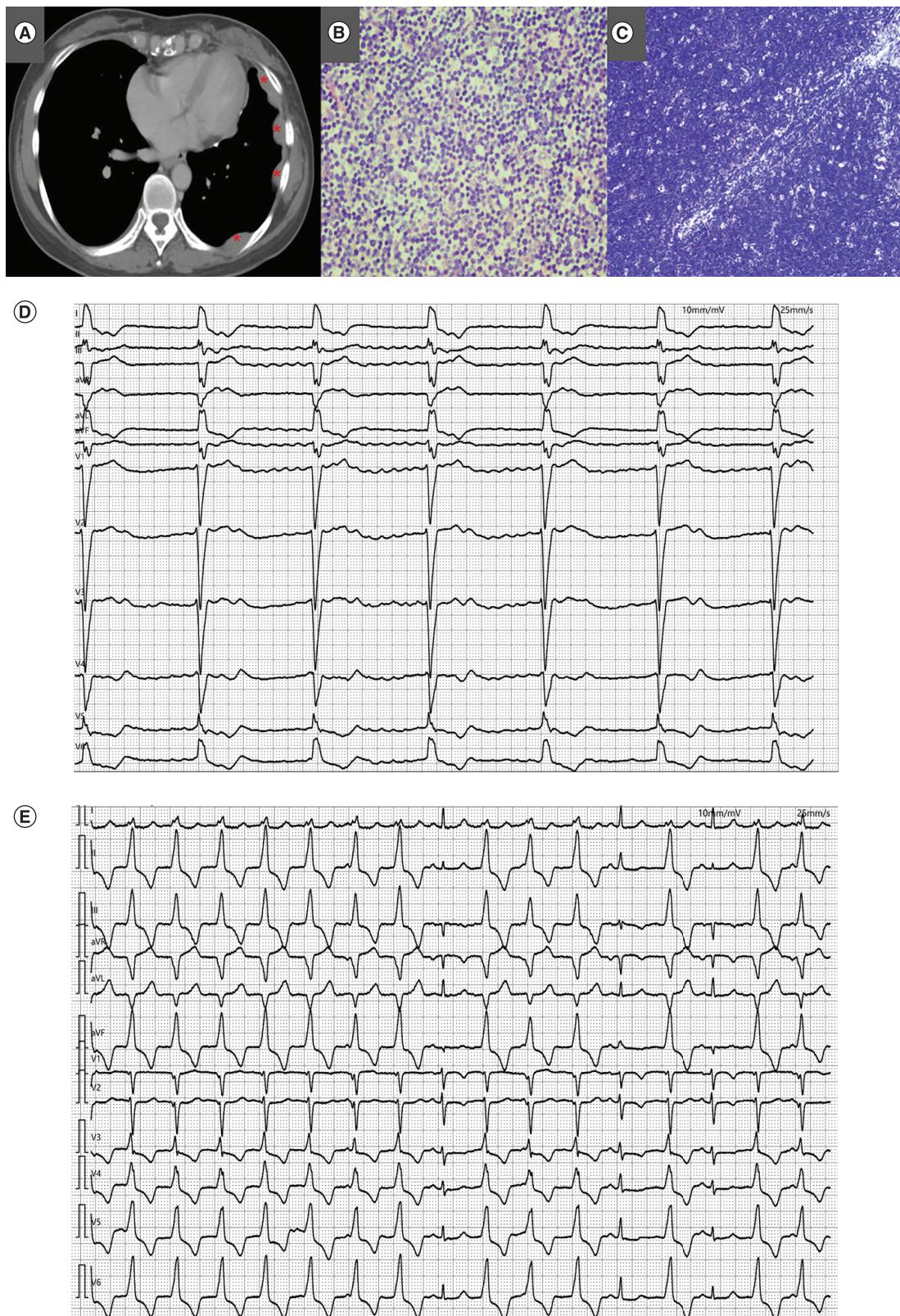


Figure 2. Characteristic of patient 2. (A) Multiple pleural and diaphragmatic metastases. **(B)** Pathological diagnosis of case 2 was WHO type B1 thymoma. **(C)** Negative PD-L1 expression. **(D & E)** Echocardiogram showed third-degree atrioventricular block and ventricular arrhythmia.

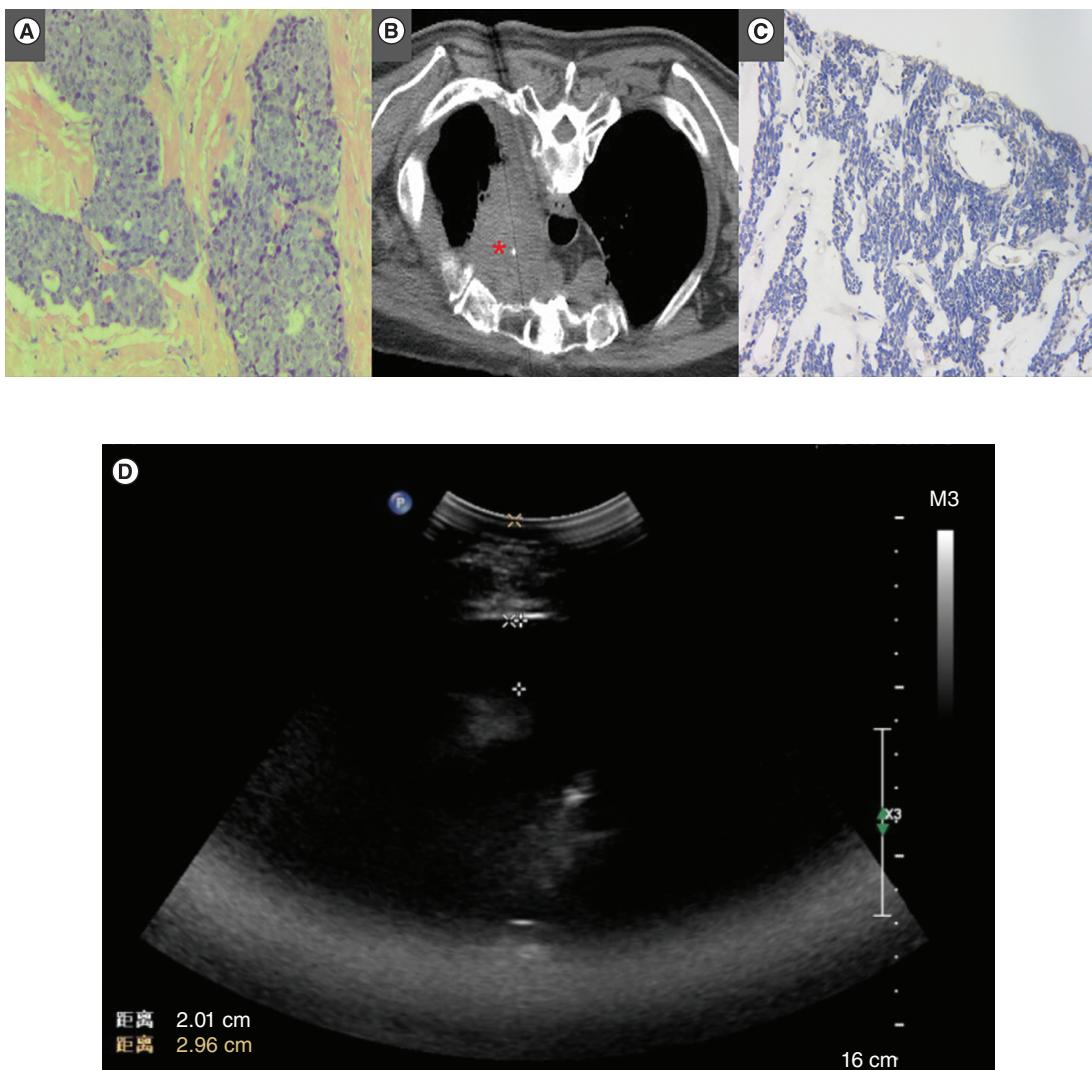


Figure 3. Characteristic of patient 3. (A) Pathological diagnosis of case 3 was WHO thymic carcinoma. (B) Progressed mass in the anterior mediastinum. (C) Negative PD-L1 expression. (D) Ultrasonographic scanning showed massive presence of pericardiac fluid.

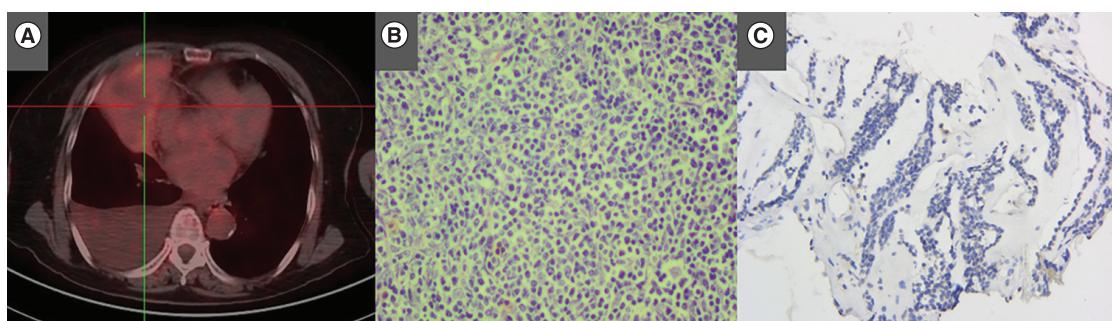


Figure 4. Characteristic of patient 4. (A) Moderate ^{18}F -fluorodeoxyglucose uptake in mediastinal mass. (B) Anterior mediastinal tumor was diagnosed as type AB. (C) Status of PD-L1 is less than 1%.

Table 2. Basic characteristic of cases.

Case	Age	Gender	Tumor type	ICIs	Basic characteristic of cases					
					PD-L1 (%)	TMB	MSI status	Lines of ICIs	RT When ICIs	Days from the first administration to death
1	56	M	B1	Sintilimab	NA	NA	NA	3	No	9
2	46	F	B1	Sintilimab	<1	0.8	MSS	4	Yes	20
3	62	F	C	Sintilimab	<1	NA	NA	4	No	11
4	77	F	AB	Pembrolizumab	<1	0.47	MSS	2	Yes	10

ICI: Immune checkpoint inhibitor.

All patients have understood all aspects of the informed consent they signed.

Discussion

Herein, we present four cases of metastatic thymomas or thymic carcinomas treated with ICIs, which resulted in a fatal storm of irAEs. On the basis of the patient characteristics summarized in Table 2: 1) the incidence of irAEs was greater in the patients with thymomas than in those without: two cases of type B1 thymomas, 1 case of type AB thymoma, and 1 case of thymic carcinoma; 2) all patients received ICIs, including pembrolizumab (one case) and sintilimab (three cases); 3) multiple previous lines of treatment (>3 lines) were administered to all cases before ICI treatment; 4) three of the four cases presented low PD-L1 expression (<1%), and the status of PD-L1 expression of the remaining case was not available; 5) The TMB and MSI status available for two cases showed low TMB (<1 mutation per Mb), and the MSI status was MSS; 6) half of the cases received radiotherapy when pembrolizumab or sintilimab was administered to improve local control; and 7) the period from the first administration of ICIs to death varied from 9 days to 20 days, with an average of 12.5 days.

Efficacy of ICIs

The anti-PD-1 antibody pembrolizumab has been evaluated in clinical trials in patients with recurrent TETs [6,7]. Trial by Cho *et al.* targeted 33 patients, of whom 26 had thymic carcinomas and seven had thymomas. Of the seven thymoma patients, two (28.6%) achieved PR, and five (71.6%) achieved SD. In 26 patients with thymic carcinoma, five (19.2%) patients achieved PR, and 14 (53.8%) patients had SD. The median progression-free survival (PFS) was 6.1 months for both groups. For both thymic carcinoma and thymoma, the median overall survival (OS) was 14.5 months and not reached, respectively [6]. Giaccone *et al.* conducted a phase II trial using pembrolizumab. Of the 40 assessable patients, the overall response rate was 22.5%, the median response duration was 22.4 months, the median PFS was 4.2 months, and the median OS was 24.9 months. The 1-year PFS and OS rates were 29% and 71%, respectively [7]. Other ICIs such as avelumab [13] and nivolumab [8] have also been investigated in TETs. Sintilimab (Innovent Biologics, Suzhou, China), a highly selective, humanized antibody, targets the PD-1 receptor [14–16]. Studies evaluating sintilimab treatment in advanced solid tumors indicated that a dose of 200 mg every 3 weeks is required to observe clinical benefit [17–19]. More than 100 trials investigating sintilimab have been registered at ClinicalTrials.gov, but no results regarding TETs have been published to date. The results of trials about other tumors encourage evaluation of the clinical efficacy of treatment with PD-1/PD-L1 inhibitors in patients with recurrent TETs, suggesting that ICI treatment is a promising option in TET patients with disease progression following at least one first-line chemotherapy regimen.

All four cases described herein received either pembrolizumab ($n = 1$) or sintilimab ($n = 3$) after having undergone ≥ 3 lines of systemic chemotherapy. In China, no PD-1 monoclonal antibodies have been approved for patients with relapsed or refractory TETs. Therefore, pembrolizumab or sintilimab treatment is appropriate for TETs because of the absence of a standard treatment for patients with TETs that have progressed following at least first-line chemotherapy.

Adverse events

Although ICIs targeting PD-1 or PD-L1 have shown good clinical efficacy in TETs, and their response rate and response duration are consistent with those of other solid tumors that have been reported, toxicity is still a major concern. Fatal adverse events caused by pembrolizumab have been reported [20,21].

Few studies evaluated the adverse events of ICIs in thymomas. Giaccone *et al.* [7] reported that toxicity is well tolerated and that mild fatigue, fever, diarrhea and rhinorrhea are the major side effects. Six patients (15%)

experienced grade 3–4 irAEs. Of these, two patients developed severe autoimmune diseases: one patient experienced severe myositis and myocarditis and required a pacemaker implantation, and the other patient developed Type I diabetes after stopping the medication [7]. A trial by Cho *et al.* showed that irAEs with severity of more than grade 3 include hepatitis (12.1%), myocarditis (9.1%), and myasthenia gravis (6.1%). Eight patients had to discontinue treatment after an adverse event [6]. Thomopoulou *et al.* reported two cases of metastatic B2/B3 thymomas treated with pembrolizumab after the initial standard chemotherapy was found ineffective. After the first treatment cycle of pembrolizumab, irAEs were triggered, including myositis, myocarditis, myasthenia gravis and death [21]. In our report, the fourth patient who was refractory to initial standard chemotherapy treatment died 10 days after the first administration of pembrolizumab.

In the ORIENT-1 trial about adult Hodgkin's lymphoma, the safety of sintilimab was controlled, which was similar to the safety of pembrolizumab and nivolumab [17]. In cases 1 to 3 of the present study, the patients who received sintilimab experienced third-degree atrioventricular block and all died due to sintilimab administration. To our knowledge, this is the first case series report describing fatal adverse events regarding sintilimab treatment, and the largest number of deaths was reported to be induced by sintilimab in TETs.

In all our cases reported herein, myocarditis resulting after ICI treatment was the main reason of death among these patients. Of all the irAEs reported to date, myocarditis has exhibited the highest mortality rate (39.7%) [22]. Overall, cardiotoxic irAEs are extremely rare. Among patients treated with nivolumab, only 0.09% experienced myocarditis [23]. In patients receiving anti-PD-1/anti-CTLA-4 combination therapy, up to 2.4% reported cardiotoxic irAEs in an independent multicenter registry [24]. Previous case reports have also observed myocarditis in patients with thymoma as a complication of ICI treatment [25,26].

A potential mechanism underlying autoimmune myocarditis may involve a common target antigen between tumor cells and cardiomyocytes, which becomes the target of activated T cells. ICI treatment causes myocardial lymphocytes to penetrate cardiac tissue, leading to heart failure and conduction abnormalities. A recent report by Johnson *et al.* [23] has provided the first molecular evidence to support this theory. The authors found that T cells, tumor cells, and cardiomyocytes share highly variable complementarity determining region-3 sequences. TETs lack a normal thymus structure and abnormal thymic epithelial cells, which result in the ineffective positive and negative selection of immature T cells. With the absence of a negative selection, autoreactive T cells are released into the circulation [27]. The presence of autoreactive T cells in the circulation increases the risk of irAEs following immunotherapy in patients with TET compared with other malignant tumors [28]. In addition, the elevated autoimmune risk has been associated with the increased levels of HLA-A24 and HLA-B8 in thymocytes [29]. Nonetheless, this model is only a hypothetical explanation. The exact mechanism underlying the development of autoreactive T cells in thymoma remains unclear.

Timing of irAEs

The median time from first administration to death was 12.5 days (range: 9–20 days) for our four cases, with a shorter time (average 10 days) to death following sintilimab treatment. A systematic review and meta-analysis conducted by Daniel *et al.* [22] showed that the median time to onset of irAE symptoms is 15 days after treatment initiation (range: 3–543 days), and the median time from symptoms to death is 32 days (range: 3–355 days). Other published reports have indicated that the average period before symptom onset varies widely from 2–32 weeks (median 10 weeks) starting after the first ICI dose [30]. Thus, these fatal events generally occurred earlier in our cases than those reported to date. We hypothesize that data from previous reports included different ICIs, such as anti-CTLA-4 anti-PD-1/PD-L1 antibodies, whereas all our patients received only the anti-PD-1 antibody, which may be associated with an earlier time of irAE onset. Furthermore, the time to irAE onset and the time from symptom onset to death after sintilimab treatment have not been reported to date. Sintilimab may have a specific timing and spectrum of irAEs, but further evidence is needed to reach this conclusion.

Immune status

The expression levels of PD-L1 and TMB in tumor cells are biomarkers of response to ICI therapy. The expression of PD-L1 in TETs has been widely reported [31–38], although it varies depending on the antibody used in IHC and the cutoff values. PD-L1 is usually expressed in 23–92% of TET tumor cells and in 36–100% of tumor cells in thymoma. These results provide a theoretical basis for the treatment of TET with PD-1/PD-L1 inhibitors. These studies advocate the clinical application of ICIs for TETs, especially in cases of high PD-L1 expression, which is common in aggressive TETs [37].

In thymus tumors, the prototype structure consists of immature and mature T cells and thus cannot reflect the actual antitumor response. Treatments such as chemotherapy or targeted medicine increase PD-L1 expression in T regulatory cells [39]. PD-L1 expression is significantly upregulated after radiotherapy in NSCLC [40], but the role of radiotherapy in upregulating PD-L1 expression in thymomas remains unclear. Given its high expression in normal thymic epithelium, PD-L1 cannot be a biomarker for thymoma [21]. Therefore, the PD-L1 status before initial treatment cannot truly express the actual immune status when ICIs are used, which can explain why the patient with low or negative PD-L1 could benefit from ICI treatment.

In the cases reported herein, the expression levels of PD-L1 and TMB were low. The expression of PD-L1 was <1% in three cases (for one case, data were not available), whereas the TMB was <1 mutation/Mb in two cases (in two cases, data were not available). To date, reports describing the correlation of fatal irAEs with the expression of PD-L1 and TMB remain lacking. Thus, whether fatal ICI-induced events are correlated with the low expression of PD-L1 and TMB has yet to be clarified. Furthermore, the MSS status in TETs has rarely been reported. The role of MSS in predicting response and/or irAE warrants further research.

Need & challenge of clinical trial for the safe administration of the ICI

No drug is approved for the treatment of TETs at present. Therefore, the off-label use of PD-1/PD-L1 blockers in TETs requires careful discussion by multidisciplinary experts and consideration of biomarkers, such as PD-L1. Future research should concentrate on strategies to select TET patients who respond to ICIs and have a low risk of developing irAEs. Possible strategies include reduction of ICI dose, identification of potential biomarkers measured before and during ICI, and measurement of circulating inflammatory and noninflammatory mediators.

Conclusion & future perspective

Despite the high risk of irAEs, ICIs have shown clinical anticancer activity in relapsed and refractory TETs. Severe irAEs, including hepatitis, myocarditis, polymyositis, pancreatitis, enteritis, bullous pemphigoid, type 1 diabetes mellitus and myasthenia gravis, are more common in thymoma than in thymic carcinomas. With the relatively high incidence of irAEs, early detection of toxicity by carefully monitoring patients is important during treatment. Myocarditis is a rare type of irAEs, but it is usually fulminant and triggers severe side effects. Clinicians should be aware of rare lethal complications. Future studies should develop effective immunotherapy strategies and identify biomarkers of response and toxicity to improve the prognosis of TET patients. Strategies to identify patients who will achieve an early response to ICIs should also be developed to select TET patients who will have a low risk of immune-related adverse events.

Summary points

- Immune checkpoint inhibitors (ICIs) exhibit clinical anticancer activity in relapsed and refractory thymic epithelial tumors despite the high risk of immune-related adverse events.
- ICIs increase the risk of developing immune-related adverse events, even fatal toxicity.
- Clinicians should be aware of rare lethal complications, especially when administering ICIs for thymoma.
- Further studies are needed to develop effective immunotherapy strategies and to identify biomarkers of response and toxicity.

Author contributions

All people who met authorship ICMJE criteria are listed as authors. H Zhu and JM Yu participated in the conception and design of this study; XQ Jing, YY Li, WX Jia, XY Zhai and J Li collected and analyzed the data and drafted the manuscript. All authors contributed to the article and read and approved the submitted version.

Financial & competing interests disclosure

This work was supported by the Innovation Project of Shandong Academy of Medical Sciences (2019–04) and the Academic Promotion Program of Shandong First Medical University [grant number: 2019ZL002]; the National Natural Science Foundation of China [grant number: 81972862]; and CSCO- 27 Pilot Cancer Research Fund [grant number: Y-2019AZZD-0352].

The authors state that they have obtained verbal and written informed consent from the patients for the inclusion of their medical and treatment history within this case report.

Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Scorsetti M, Leo F, Trama A et al. Thymoma and thymic carcinomas. *Crit. Rev. Oncol. Hematol.* 99, 332–350 (2016).
2. Engels EA. Epidemiology of thymoma and associated malignancies. *J. Thorac. Oncol.* 5(10 Suppl. 4), S260–265 (2010).
3. Marx A, Chan JK, Coindre JM et al. The 2015 World Health Organization classification of tumors of the thymus: continuity and changes. *J. Thorac. Oncol.* 10(10), 1383–1395 (2015).
- **Brief explanation: WHO Classification of thymus tumors.**
4. Kelly RJ, Petrini I, Rajan A, Wang Y, Giaccone G. Thymic malignancies: from clinical management to targeted therapies. *J. Clin. Oncol.* 29(36), 4820–4827 (2011).
5. Mandal R, Chan TA. Personalized oncology meets immunology: the path toward precision immunotherapy. *Cancer Discov.* 6(7), 703–713 (2016).
6. Cho J, Kim HS, Ku BM et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: an open-label phase II trial. *J. Clin. Oncol.* 37(24), 2162–2170 (2019).
- **Brief explanation: First data to demonstrate the activity of anti-PD-1 therapy in pretreated metastatic thymic carcinoma.**
7. Giaccone G, Kim C, Thompson J et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol.* 19(3), 347–355 (2018).
8. Katsuya Y, Horinouchi H, Seto T et al. Single-arm, multicentre, Phase II trial of nivolumab for unresectable or recurrent thymic carcinoma: PRIMER study. *Eur. J. Cancer* 113, 78–86 (2019).
9. June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? *Nat. Med.* 23(5), 540–547 (2017).
10. Michot JM, Bigenwald C, Champiat S et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur. J. Cancer* 54, 139–148 (2016).
11. Brahmer JR, Lacchetti C, Schneider BJ et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J. Clin. Oncol.* 36(17), 1714–1768 (2018).
- **Brief explanation: Treatment of irAEs when ICIs used.**
12. De Velasco G, Je Y, Bossé D et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol. Res.* 5(4), 312–318 (2017).
13. Rajan A, Heery CR, Thomas A et al. Efficacy and tolerability of anti-programmed death-ligand 1 (PD-L1) antibody (avelumab) treatment in advanced thymoma. *J. Immunother. Cancer* 7(1), 269 (2019).
14. Hoy SM. Sintilimab: first global approval. *Drugs* 79(3), 341–346 (2019).
15. Wang J, Fei K, Jing H et al. Durable blockade of PD-1 signaling links preclinical efficacy of sintilimab to its clinical benefit. *MAbs* 11(8), 1443–1451 (2019).
16. Kaplon H, Reichert JM. Antibodies to watch in 2019. *MAbs* 11(2), 219–238 (2019).
17. Shi Y, Su H, Song Y et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, Phase 2 trial. *Lancet Haematol.* 6(1), e12–e19 (2019).
18. Ansell SM. Sintilimab: another effective immune checkpoint inhibitor in classical Hodgkin lymphoma. *Lancet Haematol.* 6(1), e2–e3 (2019).
19. Yao X, Du N, Hu S, Wang L, Gao J. Rapid advances in research on and development of anticancer drugs in China. *Biosci. Trends* 13(5), 461–463 (2019).
20. March KL, Samarin MJ, Sodhi A, Owens RE. Pembrolizumab-induced myasthenia gravis: a fatal case report. *J. Oncol. Pharm. Pract.* 24(2), 107815521668738 (2017).
21. Konstantina T, Konstantinos R, Anastasios K et al. Fatal adverse events in two thymoma patients treated with anti-PD-1 immune check point inhibitor and literature review. *Lung Cancer* 135, 29–32 (2019).
22. Wang DY, Salem JE, Cohen JV et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol.* 4(12), 1721–1728 (2018).
- **Brief explanation: Focus on fatal irAEs with ICIs.**
23. Johnson DB, Balko JM, Compton ML et al. Fulminant myocarditis with combination immune checkpoint blockade. *N. Engl. J. Med.* 375(18), 1749–1755 (2016).
24. Mahmood SS, Fradley MG, Cohen JV et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J. Am. Coll. Cardiol.* 71(16), 1755–1764 (2018).

25. So H, Ikeguchi R, Kobayashi M, Suzuki M, Shimizu Y, Kitagawa K. PD-1 inhibitor-associated severe myasthenia gravis with necrotizing myopathy and myocarditis. *J. Neurol. Sci.* 399, 97–100 (2019).
26. Chen Q, Huang DS, Zhang LW, Li YQ, Wang HW, Liu HB. Fatal myocarditis and rhabdomyolysis induced by nivolumab during the treatment of type B3 thymoma. *Clin. Toxicol.* 56(7), 667–671 (2018).
27. Weksler B, Lu B. Alterations of the immune system in thymic malignancies. *J. Thorac. Oncol.* 9(9 Suppl. 2), S137–S142 (2014).
28. Zhao C, Rajan A. Immune checkpoint inhibitors for treatment of thymic epithelial tumors: how to maximize benefit and optimize risk? *Mediastinum* 3, 35 (2019).
- **Brief explanation: Concern about maximizing benefit and optimizing risk of ICIs.**
29. Shelly S, Agmon-Levin N, Altman A, Shoenfeld Y. Thymoma and autoimmunity. *Cell Mol. Immunol.* 8(3), 199–202 (2011).
30. Jain V, Bahia J, Mohebtash M, Barac A. Cardiovascular complications associated with novel cancer immunotherapies. *Curr. Treat Options Cardiovasc. Med.* 19(5), 36 (2017).
31. Padda SK, Riess JW, Schwartz EJ *et al.* Diffuse high intensity PD-L1 staining in thymic epithelial tumors. *J. Thorac. Oncol.* 10(3), 500–508 (2015).
32. Katsuya Y, Fujita Y, Horinouchi H, Ohe Y, Watanabe S, Tsuta K. Immunohistochemical status of PD-L1 in thymoma and thymic carcinoma. *Lung Cancer* 88(2), 154–159 (2015).
33. Yokoyama S, Miyoshi H, Nishi T *et al.* Clinicopathologic and prognostic implications of programmed death ligand 1 expression in thymoma. *Ann. Thorac. Surg.* 101(4), 1361–1369 (2016).
34. Yokoyama S, Miyoshi H, Nakashima K *et al.* Prognostic value of programmed death ligand 1 and programmed death 1 expression in thymic carcinoma. *Clin. Cancer Res.* 22(18), 4727–4734 (2016).
35. Marchevsky AM, Walts AE. PD-L1, PD-1, CD4, and CD8 expression in neoplastic and nonneoplastic thymus. *Hum. Pathol.* 60, 16–23 (2017).
36. Weissferdt A, Fujimoto J, Kalhor N *et al.* Expression of PD-1 and PD-L1 in thymic epithelial neoplasms. *Mod. Pathol.* 30(6), 826–833 (2017).
37. Arbour KC, Naidoo J, Steele KE *et al.* Expression of PD-L1 and other immunotherapeutic targets in thymic epithelial tumors. *PLOS ONE* 12(8), e0182665 (2017).
38. Owen D, Chu B, Lehman AM *et al.* Expression patterns, prognostic value, and intratumoral heterogeneity of PD-L1 and PD-1 in thymoma and thymic carcinoma. *J. Thorac. Oncol.* 13(8), 1204–1212 (2018).
39. Thomas A, Rajan A, Berman A *et al.* Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. *Lancet Oncol.* 16(2), 177–186 (2015).
40. Yoneda K, Kuwata T, Kanayama M *et al.* Alteration in tumoural PD-L1 expression and stromal CD8-positive tumour-infiltrating lymphocytes after concurrent chemo-radiotherapy for non-small cell lung cancer. *Br. J. Cancer* 121(6), 490–496 (2019).

