Introduction

The advent of immunotherapy is rapidly changing the treatment paradigm for various cancers and improving patient outcomes. Underlying these advances is a clearer understanding of the complex relationship between cancer and the immune system. The development of cancer is fundamentally a disorder of immune surveillance and an inability to eliminate neoplastic cells (1). Anti-cancer immunity is influenced by features of the tumor and tumor microenvironment, such as tumor-associated antigen and major histocompatibility complex (MHC) antigen expression, cytokine levels, relative proportions of immune stimulatory and immunosuppressive cells, and the status of immune checkpoints, as well as host and environmental factors (2).

Based on this knowledge, a number of immunotherapeutic interventions have been developed for treatment of advanced...
cancers including vaccines, adoptive T-cell therapy and immune checkpoint blockade (3). Antibodies targeting the immunosuppressive checkpoints, programed death-1 (PD-1) or its ligand (PD-L1) are now an integral component of cancer therapy and are being widely evaluated in combination with other treatment modalities, including chemotherapy, radiation therapy and other forms of immunotherapy (4). Emerging data provide proof of long-term safety and durable benefit of immunotherapy with an improvement in survival in patients with advanced cancers (5,6).

In this paper we review the role of immunotherapy for management of advanced thymic epithelial tumors (TETs) and discuss the impact of unique aspects of TET biology on the risks and potential benefits of immune modulation. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/med-20-62).

Data sources

In order to select data for inclusion in this narrative review, we performed a literature search using the National Library of Medicine’s PubMed® database. Selection of papers was limited to the English language but there were no limits on the type of report or the time of publication.

TETs and the immune system

The thymus gland plays a key role in development of normal immunological function including the body’s ability to recognize its own tissue and develop immunological self-tolerance (7,8). This process involves the migration of lymphoid progenitor cells into the thymus followed by a series of steps that culminates in the formation of CD4+CD8+ double positive cells that express a functional T cell receptor (TCR). Subsequently, a subset of T cells expressing either CD4 or CD8 enter the thymic medulla and are exposed to organ-specific antigens. Autoreactive T cells undergo apoptosis and the remainder enter the peripheral circulation (9). Medullary thymic epithelial cell expression of tissue-restricted antigens is controlled by the transcription factors, AIRE (autoimmune regulator) and FezF2 (8,10,11). A breakdown in immunological tolerance results in entry of autoreactive T cells into the peripheral circulation and increases the risk for development of autoimmunity and immunodeficiency.

The association between TETs, especially thymomas, and paraneoplastic autoimmunity is well recognized (12). Defective immune tolerance in patients with TETs is attributed to multiple factors including decreased expression of AIRE and FezF2, altered thymic architecture and downregulation of MHC class 2 antigens (12).

An additional mechanism for development of paraneoplastic autoimmunity in patients with TETs appears to rely on structural similarities between antigens overexpressed by neoplastic cells and autoantigens expressed on target organs by the process of molecular mimicry. Data from The Cancer Genome Atlas program for thymomas reveals overexpression of the mid-sized neurofilament gene (NEF) in thymomas associated with myasthenia gravis (MG), which shares sequences coding for acetylcholine receptor (AChR) and titin epitopes that are associated with MG (13).

In addition to autoimmune paraneoplastic disease, T-cell dysfunction in patients with TETs can also manifest clinically in the form of an immunodeficiency state. Acquired T-cell deficiency can be accompanied by hypogammaglobulinemia and increase the risk of opportunistic infections (14).

Determinants of response to immune checkpoint inhibitors (ICIs)

Despite the widespread use of ICIs for cancer therapy, a large proportion of patients with advanced cancers do not derive significant clinical benefit. This observation has spurred the development of predictive biomarkers to help identify patients most likely to benefit from treatment (15). Tumor cell PD-L1 expression and tumor mutation burden (TMB) have been widely evaluated as biomarkers of response to ICIs (16). Tumors with high PD-L1 expression and/or high TMB are more likely to respond to ICI therapy (17). However, the predictive value of these biomarkers is not uniform across tumor types (15).

Microsatellite instability caused by defects in DNA mismatch repair (MMR) results in a high TMB and an increase in tumor-infiltrating lymphocytes (18). Consequently, tumors with MMR deficiency are more likely to respond to immune checkpoint blockade, as has been observed in clinical trials (19). Higher response rates and longer survival following treatment with ICIs has also been seen in patients with concurrent mutations in genes involved in other DNA damage repair pathways, such as base excision repair and homologous recombination (20).

An 18-gene T-cell inflamed gene expression profile (GEP) that reflects a T-cell activated tumor microenvironment has been evaluated as a potential biomarker of response to
ICIIs and is shown to be associated with response and an improvement in survival with pembrolizumab across various tumor types (17).

To improve selection of patients for immunotherapy, several novel predictive biomarkers are under active investigation. These include somatic mutations, HLA diversity, cytokines such as interleukin-6, TCR clonality and host factors such as the gut microbiome (15,21).

**Rationale for use of ICIIs for treatment of TETs**

PD-L1 expression is common across the histological spectrum of TETs with higher expression observed more frequently in clinically aggressive histological subgroups (22,23). However, TETs have a low TMB and microsatellite instability is extremely rare (13,24,25). Despite a low TMB, alterations in genes involved in DNA repair such as BRCA2, BAP1 and ATM have been observed in up to 13% of recurrent TETs (26,27). It is unclear if these genomic alterations increase the likelihood of response to immune checkpoint blockade.

In order to establish a rationale for use of immunotherapy in patients with recurrent TETs, recent research has focused on the unique biology of thymoma and thymic carcinoma. Functional analysis of CD4 and CD8 single-positive T cells by flow cytometry has revealed an increased proportion of Tim-3- and CD103-expressing T cells in type B3 thymoma and thymic carcinoma. Cytokine production and cytotoxicity of effector T cells was enhanced to a greater degree by the PD-1 inhibitor, nivolumab in these histological subtypes (28). Preclinical studies have also shown significant enhancement of antitumor activity of ICIIs in the presence of Aire-deficiency, which is commonly observed in thymomas (29).

These observations, coupled with tumor cell PD-L1 expression, provide a rationale for evaluation of ICIIs in TETs despite low TMB and absence of microsatellite instability.

**Immunotherapy for TETs**

The safety and clinical activity of immunotherapy for TETs has been reported in five completed prospective trials, including four studies that have evaluated PD-1/PD-L1-directed monoclonal antibodies and one trial that evaluated a WT-1-based peptide vaccine.

**Clinical activity**

Between December 2013 to October 2014, 7 patients with recurrent thymoma and 1 patient with recurrent thymic carcinoma were enrolled in a phase 1 dose-escalation study of the anti-PD-L1 antibody, avelumab (NCT01772004) and treated at two dose levels (10 or 20 mg/kg) (30). Two (29%) patients had a confirmed partial response and 5 (63%) patients had stable disease, including 2 individuals who met response evaluation criteria in solid tumors (RECIST) for an unconfirmed partial response. Two responses occurred at each dose level tested and 3 of 4 responses occurred after administration of a single dose of avelumab. The duration of response ranged from 4 to 17 weeks, despite discontinuation of treatment after a single dose in 3 of 4 patients. These results provided initial evidence of anti-tumor activity of PD-L1-directed therapy in relapsed thymoma.

From March 2015 to December 2016, 41 patients with relapsed thymic carcinoma were enrolled in a single-arm phase 2 trial of pembrolizumab (anti-PD-1 antibody; NCT02364076) and received 200 mg intravenously every 3 weeks for up to 2 years (31). The overall response rate (ORR) was 22.5%. The median duration of response (DOR) was 22.4 months, median progression free survival (PFS) was 4.2 months and median overall survival (OS) was 24.9 months. The clinical activity of pembrolizumab in recurrent TETs was confirmed in a subsequent phase 2 trial that enrolled 26 patients with relapsed thymic carcinoma and 7 patients with relapsed thymoma (NCT02607631) (32). The ORR was 28.6% in patients with thymoma and 19.2% in patients with thymic carcinoma. The median DOR was not reached in patients with thymoma and it was 9.7 months in patients with thymic carcinoma. Median PFS was 6.1 months for both groups. Median OS was not reached for patients with thymoma and it was 14.5 months for the thymic carcinoma cohort.

Nivolumab, an anti-PD-1 antibody, has been evaluated in patients with recurrent thymic carcinoma in a single-arm phase 2 clinical trial (PRIMER study) (33). Fifteen patients were enrolled and received nivolumab 3 mg/kg intravenously every 2 weeks. No objective responses were observed in this study. The median PFS was 3.8 months and median OS was 14.1 months.

Oji and colleagues have evaluated a novel immunotherapeutic intervention with a WT1 peptide vaccine in patients with advanced TETs (34). Fifteen patients (4 thymoma, 11 thymic carcinoma) were enrolled in a phase 2 trial and received a 9 mer-WT1-derived peptide vaccine intradermally once a week. After completion of a planned study period of 3 months, treatment was continued at
2-4-week intervals until disease progression or development of intolerable adverse events. Although no objective responses were observed in this study, 75% of patients achieved disease stabilization and a majority of patients demonstrated a WT1-specific immune response. The median duration of treatment was 133 days in patients with recurrent thymic carcinoma and 683 days in patients with recurrent thymoma.

These observations provide evidence of the clinical activity of immunotherapy in patients with relapsed TETs and are summarized in Table 1. However, clinical benefit is not uniform and highlights the need to develop biomarkers to identify patients most likely to benefit from treatment.

### Biomarkers for response to immunotherapy

Patients enrolled in 3 of the 5 clinical trials described above experienced an objective response to treatment. In the trials evaluating pembrolizumab, high PD-L1 expression (defined as > 50% tumor cell PD-L1 staining by immunohistochemistry) was associated with higher response rates and longer survival (31,32). However, it should be noted that the majority of patients enrolled in these trials had thymic carcinoma. It is unclear if PD-L1 expression is equally effective in predicting response and survival in patients with advanced thymoma.

T-cell gene expression profiling was conducted in the study evaluating pembrolizumab in thymic carcinoma (NCT02364076) and revealed higher expression of the 18-gene T-cell-inflamed interferon-g gene expression profile among responders (31). There was no correlation between somatic mutations detected by targeted exome sequencing and response to treatment (31).

In the phase I trial of avelumab, responders had a higher pre-treatment absolute lymphocyte count, lower frequencies of B cells, regulatory T cells, conventional dendritic cells, and natural killer cells and higher baseline TCR diversity (30). All responders also developed immune-related adverse events (irAEs). These observations are illustrated in Figure 1.

### Safety

One of the biggest challenges associated with the use of immunotherapy for TETs is the risk for development of potentially life-threatening immune-mediated toxicity.

Results from prospective clinical trials and several case reports confirm the increased risk of irAEs and highlight the predisposition toward muscle and neuromuscular toxicity (30-36). Polymyositis (all grades) has been observed in 8% to 57% of TET patients treated with ICIs. Corresponding figures for myocarditis and myasthenia gravis are 5% to 57% and 3% to 14%, respectively, with a higher incidence in patients with advanced thymoma (30-32). Musculoskeletal

<p>| Table 1 Clinical activity of immunotherapy in relapsed thymic epithelial tumors |
|---------------------------------|----------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab (32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoma</td>
<td>7</td>
<td>28.6</td>
<td>6.1</td>
<td>Not reached</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>26</td>
<td>19.2</td>
<td>6.1</td>
<td>14.5</td>
</tr>
<tr>
<td>Pembrolizumab (31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>40</td>
<td>22.5</td>
<td>4.2</td>
<td>24.9</td>
</tr>
<tr>
<td>Avelumab (30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoma</td>
<td>7</td>
<td>28.5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>15</td>
<td>0</td>
<td>3.8</td>
<td>14.1</td>
</tr>
<tr>
<td>Nivolumab (33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>4</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>WT1 peptide vaccine (34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoma</td>
<td>4</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>11</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; NR, not reported.
and neuromuscular irAEs generally occur early and have been observed within 1–6 weeks of initiation of ICI therapy (30-32). It should be noted that the elevated risk of immune toxicity is present across the histological spectrum of TETs and can be observed in individuals with thymic carcinoma as well (31,32,36). Furthermore, muscle and neuromuscular toxicity in TET patients is not limited to ICI therapy alone and has been observed in patients receiving a cancer vaccine. One of 4 patients with thymoma receiving a WT1 peptide vaccine developed myasthenia gravis 26 months after initiation of treatment (34). Compared with observations of neuromuscular complications in patients with TETs receiving ICIs, the delayed onset of myasthenia gravis in this case highlights the need for close monitoring for immune toxicity throughout the course of treatment.

In contrast, neuromuscular and cardiac toxicity is uncommon in patients with non-thymic cancers receiving ICIs. The incidence of ICI-induced neurological adverse events is 1% or less in large studies (37). Myopathies are observed in less than 1% of patients receiving PD-1-directed anticancer therapy, whereas myocarditis has been reported in 0.4% to 1% of patients receiving ICIs (38-40).

Additionally, with the exception of myasthenia gravis, neuromuscular disorders are uncommon manifestations of paraneoplastic autoimmunity in patients with TETs. The prevalence of polymyositis is 1% to 5% and paraneoplastic myocarditis is observed in fewer than 1% of patients with thymoma (12).

TET patients receiving ICIs have also been observed to develop other relatively uncommon irAEs such as type 1 diabetes mellitus, sicca syndrome and acquired coagulopathy (Figure 2) (31,41,42). Table 2 lists irAEs reported in published clinical trials of immunotherapy in relapsed TETs.

Taken together, these observations are indicative of an increased risk of immune-mediated toxicity in patients with TETs receiving immunotherapy, regardless of the treatment modality and histological characteristics of the tumor and stress the need for extreme caution while using immunotherapy for treatment of TETs.

**Biomarkers for toxicity**

The reasons for an increased incidence of irAEs in patients with TETs receiving immunotherapy are incompletely understood, although it appears to be fundamentally related to defective immune self-tolerance and persistence of autoreactive T-cells.

Clinical trials of avelumab and pembrolizumab provide early evidence of potential biomarkers of toxicity to

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**Figure 1** Emerging biomarkers for response of thymic epithelial tumors to immune checkpoint inhibitors. PD-L1, programed death ligand-1; TCR, T cell receptor; irAEs, immune-related adverse events; *, tumor-related biomarker evaluation in prospective clinical trials is largely limited to thymic carcinoma.
Figure 2 Immune-related adverse events observed in patients with thymic epithelial tumors receiving immunotherapy. Immune checkpoint inhibition increases the risk for development of a wide spectrum of immune-related adverse events in patients with thymic epithelial tumors (30-33). A predisposition toward muscle and neuromuscular toxicity is observed, which can be severe and life-threatening. GI, gastrointestinal.

immunotherapy in patients with thymoma and thymic carcinoma with no clinical history of paraneoplastic autoimmunity.

In two trials evaluating pembrolizumab in relapsed TETs, there was no correlation between development of irAEs and the degree of PD-L1 expression or the presence of somatic mutations detected by targeted exome sequencing (31,32).

However, patients with relapsed thymoma who developed immune-related myositis following treatment with avelumab were found to have detectable titers of AChR-binding autoantibodies prior to start of treatment, whereas patients who did not develop myositis had no pre-treatment AChR autoantibodies (43). In addition, patients who developed irAEs also had profound B-cell cytopenia and lower levels of regulatory T cells and conventional dendritic cells (30,43). Unsupervised hierarchical clustering of major peripheral blood mononuclear cell (PBMC) subsets prior to treatment revealed an immune phenotype that was associated with development of autoimmunity and TCR diversity in pretreatment PBMCs was higher in patients experiencing irAEs (30).

If validated in larger studies, these observations can help select patients with thymoma and thymic carcinoma for immunotherapy who are at lower risk for development of irAEs.

Mitigation of immune toxicity

Although careful consideration of clinical history and the development of predictive biomarkers might potentially lessen the risk of irAEs in patients with thymoma and thymic carcinoma, it is unlikely that these risks can be eliminated due to the underlying biology of these diseases. Hence, it is important to develop other risk mitigation strategies such as prophylactic use of immunosuppressants.
Table 2 Immune-related adverse events in patients with relapsed thymic epithelial tumors receiving immunotherapy

<table>
<thead>
<tr>
<th>irAE, n [%]</th>
<th>Pembrolizumab (32)</th>
<th>Pembrolizumab (31)</th>
<th>Avelumab (30)</th>
<th>Nivolumab (33)</th>
<th>WT1 peptide vaccine (34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thymoma (n=7)</td>
<td>Thymic ca (n=26)</td>
<td>Thymoma (n=7)</td>
<td>Thymic ca (n=15)</td>
<td>Thymoma (n=4)</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>0</td>
<td>0</td>
<td>3 [8]</td>
<td>4 [57]</td>
<td>3 [20]</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>3 [43]</td>
<td>0</td>
<td>2 [5]</td>
<td>4 [57]</td>
<td>0</td>
</tr>
<tr>
<td>Subacute myoclonus</td>
<td>0</td>
<td>1 [4]</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 [14]</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>1 [14]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enteritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 [14]</td>
<td>0</td>
</tr>
<tr>
<td>Colitis†</td>
<td>1 [14]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 [20]</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>0</td>
<td>1 [3]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nephritis†</td>
<td>1 [14]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 [13]</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 [7]</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>0</td>
<td>0</td>
<td>1 [3]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other skin conditions</td>
<td>2 [29]</td>
<td>5 [19]</td>
<td>0</td>
<td>0</td>
<td>4 [27]</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 [25]</td>
</tr>
</tbody>
</table>

† includes three cases described using the term “diarrhea”; ‡ represents eight cases with aspartate transaminase elevation (AST) of any grade and three cases with alanine transaminase (ALT) elevation of any grade (etiology not defined and unclear if three subjects had concurrent elevation of AST and ALT); † represents one case described using the term “creatinine increased”; * includes one case of hypothyroidism; ‡ includes 11 cases described using the terms “dermatitis”, “skin rash” and “pruritis”. irAE, immune-related adverse event; ca, carcinoma.

in conjunction with immunotherapy and strategies to rechallenge patients who have experienced immune toxicity previously (44).

There is a growing body of data on the concurrent use of immunosuppression with immunotherapy. In a small series of five patients with solid tumors who developed immune-related enterocolitis upon treatment with ICIs, either as monotherapy or in combination, concurrent treatment with the tumor necrosis factor (TNF)-α inhibitor, infliximab and ICIs was found to be safe and prevent further episodes of immune-related enterocolitis (45). A similar approach using cyclosporine A to prevent muscle-related immune toxicity in patients with relapsed TETs is under investigation in an ongoing phase II trial of avelumab (NCT03076554). The effect of concurrent immunosuppression on the anti-tumor activity of ICIs remains to be determined.

The safety of resuming immunotherapy after resolution of an initial episode of immune-mediated toxicity has been evaluated in a few recently reported studies. No further episodes of irAEs were observed upon resumption of ICIs in 45% to 66% of patients evaluated in these studies indicating the feasibility of rechallenging patients with immunotherapy after resolution of irAEs (46–49). However, it should be stressed that the decision to resume immunotherapy should be based on the nature and severity of the initial episode of immune toxicity and is generally not recommended for patients who develop severe or life-threatening irAEs, such as myocarditis.
Future directions

ICIs have been largely successful in eliciting durable responses and improving survival of patients with several advanced cancers, including relapsed TETs. Clinical trials are currently underway to evaluate combinations of ICIs with other systemic therapies, including targeted therapies and other forms of immunotherapy in an effort to improve clinical outcomes (50). Ongoing trials evaluating immunotherapy combinations in patients with thymic cancers are listed in Table 3.

Current research is also focused on identifying biomarkers of response and toxicity to ICIs (15,21). In patients with thymoma, the presence of detectable AChR-binding autoantibodies, B-cell cytopenia and high TCR diversity at baseline appear to be associated with an increased risk for development of immune toxicities (30,43). Validation of these results in larger clinical trials and evaluation of novel biomarkers such as the tumor mutational profile and the gut microbiome holds the promise of improving the safety profile of immunotherapy for thymic cancers and identifying patients most likely to benefit from treatment.

Other clinical questions that warrant further investigation include the ability to use immunotherapy for treatment of TET patients with associated autoimmune paraneoplastic diseases and the feasibility of rechallenging TET patients with immunotherapy after resolution of a previous episode of immune-mediated toxicity. There is also a pressing need to evaluate the use of immunosuppressive drugs concurrently with immunotherapy for primary or secondary prophylaxis of irAEs in future clinical trials.

Conclusions

The clinical activity of ICIs in patients with relapsed thymoma and thymic carcinoma has been demonstrated in prospective clinical trials with several patients achieving durable responses. Immunotherapy also appears to improve survival compared with currently available treatments for patients with recurrent disease. However, treatment can be associated with the development of severe and life-threatening immune toxicity, especially in patients with thymoma. Hence, we recommend consideration of immunotherapy for treatment of TETs in the context of clinical trials with close monitoring for and aggressive management of irAEs. Ongoing advances in biomarker research increase the likelihood of identifying patients likely...
to benefit from treatment with a reduced risk of developing severe irAEs. Several unanswered questions related to clinical management of immune-mediated toxicity are being addressed in ongoing clinical trials and hold the promise of making the use of immunotherapy feasible and safe for patients with recurrent thymoma and thymic carcinoma.

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