



The role of immune checkpoint blockade for treatment of thymic epithelial tumors—a delicate balance between efficacy and side effects

Chul Kim, Giuseppe Giaccone

Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Giuseppe Giaccone, MD, PhD. Associate Director for Clinical Research, Professor of Medical Oncology and Pharmacology, Lombardi Comprehensive Cancer Center, Georgetown University, 3970 Reservoir Road, Washington, DC 20007, USA. Email: gg496@georgetown.edu.

Abstract: Therapeutic options for patients with unresectable or metastatic thymic epithelial tumors (TETs) are limited. There is no approved treatment for patients with advanced TETs whose disease has progressed after first-line platinum-based chemotherapy. Immune checkpoint inhibitors (ICIs) that target the programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway have been shown to be effective in a number of tumor types and have gained approval for multiple indications. Emerging evidence from clinical trials suggests that immune checkpoint blockade may be a viable therapeutic option for patients with TETs. Anti-PD-1/PD-L1 antibodies are active in a fraction of patients with advanced TETs with objective response rates (ORRs) ranging between 20–25%. As observed in other tumor types, responses to anti-PD-1/PD-L1 therapy tend to be durable in TETs. The incidence of serious immune-related adverse events (irAEs) however is higher in TETs than in other tumor types, necessitating vigilant monitoring of adverse events (AEs). Future studies of ICIs in patients with TETs should focus on developing more effective immunotherapy strategies, defining subsets of patients who are likely to benefit from immune checkpoint therapy, and potentially identifying patients at higher risk of autoimmune toxicity.

Keywords: Thymic carcinoma; thymoma; immune checkpoint inhibitor (ICIs)

Received: 06 April 2018; Accepted: 18 April 2018; Published: 06 May 2018.

doi: 10.21037/med.2018.04.05

View this article at: <http://dx.doi.org/10.21037/med.2018.04.05>

Thymic epithelial tumors (TETs) are malignancies that arise from thymic epithelial cells. Despite being one of the most common anterior mediastinal primary tumors, TETs are rare. The incidence of TETs in the U.S. is 0.13 cases per 100,000 person-years based on Surveillance, Epidemiology, and End Results (SEER) cancer registries (1). TETs are categorized into thymomas and thymic carcinomas according to the World Health Organization (WHO) pathologic classification (2). Compared with thymomas, thymic carcinomas behave more aggressively with a tendency to metastasize and usually present with advanced disease (Masaoka stage III or IV) (3). The mainstay of treatment for unresectable or metastatic

thymic carcinomas is platinum-based chemotherapy such as cisplatin/doxorubicin/cyclophosphamide and carboplatin/paclitaxel (4). There are no standard treatments after failure of first-line chemotherapy. Targeted therapies such as sunitinib and everolimus have some activity, but responses are usually short-lived in patients previously treated with platinum-based chemotherapy (5,6).

Immune checkpoint inhibitors (ICIs) that stimulate the immune system by blocking the inhibitory anti-programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway have proven to be effective in a broad array of tumor types. Several studies have demonstrated that PD-L1 expression, the most widely used

predictive biomarker of response to anti-PD-1/PD-L1 therapy, is high in TETs (7-10). Tumor mutations are more frequent in thymic carcinomas than in thymomas (11). In addition, thymic carcinomas are not frequently associated with autoimmune diseases such as myasthenia gravis and pure red cell aplasia that are not uncommon in patients with thymomas (4). These considerations provided the rationale for investigating the role of immune checkpoint blockade in the treatment of thymic carcinomas.

Recently, we published the results of a phase II study of pembrolizumab, an anti-PD-1 antibody, in patients with advanced refractory or recurrent thymic carcinomas (12). Patients with progressive disease who have had at least one line of chemotherapy were eligible. Those with a history of autoimmune disorders were excluded. Study treatment consisted of pembrolizumab 200 mg intravenously every 3 weeks up to 2 years. The primary endpoint was objective response rate (ORR) with secondary endpoints of progression-free survival (PFS) and overall survival (OS). A total of 40 patients were enrolled and treated with pembrolizumab. The majority of the patients (97.5%) had stage IV disease. The median number of prior lines of systemic therapy was 2 (range, 1–6). The ORR was 22.5% (95% CI: 10.8–38.5) with 1 (3%) patient achieving a complete response. Twenty-one (53%) patients had stable disease. Responses were rapid and durable with median time to response of 6 weeks (range, 6–24 weeks) and median duration of response of 22.4 months (95% CI: 12.3–34.7 months), respectively. Median PFS and OS were 4.2 months (95% CI: 2.9–10.3 months) and 24.9 months (95% CI: 15.5–not reached), respectively. Pre-treatment tumor samples were analyzed to determine whether PD-L1 expression and an 18-gene T-cell-inflamed interferon-gamma signature are predictive of treatment outcomes. In 10 patients with high PD-L1 expression, defined as positive staining in at least 50% of tumor cells, 6 (60%) achieved a response. On the contrary, among 27 patients with PD-L1 expression less than 50%, only 3 (11%) patients achieved a response. Expression of the interferon-gamma signature was also significantly higher in responders than in non-responders. In addition, there were significant correlations between PFS and OS, and PD-L1 expression and the interferon-gamma signature.

While the treatment was well tolerated with most adverse events (AEs) being grade 1 or 2, it should be noted that 6 (15%) patients developed one or more severe immune-related AEs (irAEs). Severe irAEs included hepatitis, myocarditis, polymyositis, bullous pemphigoid,

diabetes mellitus type 1, and myasthenia gravis. Severe irAEs were resolved with treatment interruption and immunosuppressant agents, mainly corticosteroids. There was no treatment-related death. Two patients who developed myocarditis and myositis underwent placement of pacemaker. Notably, in one patient who developed myocarditis and myositis, a T-cell clone which was present in pre-treatment blood increased in post-treatment blood, and was also found in tumor and muscle biopsy samples, raising the speculation that an epitope shared between tumor and normal tissue might have been responsible for the development of myocarditis.

A few other studies have reported the safety and efficacy of anti-PD-1/PD-L1 therapy for the treatment of TETs (*Table 1*). A phase II trial of pembrolizumab in Korean patients with TETs (7 thymomas, 26 thymic carcinomas) whose disease progressed after platinum-containing chemotherapy showed a comparable ORR of 23.1% in patients with thymic carcinoma and an ORR of 28.6% in patients with thymomas (13). Patients with a history of active autoimmune disease requiring systemic treatment within the past 1 year were excluded, but 8 (24.2%) patients (5 thymomas, 3 thymic carcinomas) experienced severe irAEs resulting in treatment discontinuation. A trial of avelumab, an anti-PD-L1 antibody, in patients with TETs (7 thymomas, 1 thymic carcinoma) showed 2 (25%) confirmed partial responses (14). Severe irAEs were observed in 5 (62.5%) patients, three of which were myocarditis.

In summary, anti-PD-1/PD-L1 therapy has anticancer activity against TETs with ORRs ranging between 20–25%. Durable responses observed in responders make anti-PD-1/PD-L1 blockade an attractive therapeutic approach in this patient population. The use of anti-PD-1/PD-L1 therapy for the treatment of TETs is associated with higher frequency of irAEs. While most irAEs were manageable with immunosuppressant agents such as corticosteroids, early detection of irAEs through careful monitoring of patients is necessary. Several ongoing studies including a study of pembrolizumab and epacadostat, an indoleamine 2,3-dioxygenase-1 (IDO1) inhibitor at our institution (NCT02364076) will shed further light on the safety and efficacy of immune check point therapy in TETs (*Table 2*). Future research should concentrate on developing more effective immunotherapy strategies and identifying biomarkers of response and toxicity to improve outcomes in patients suffering from TETs.

Table 1 Summary of clinical trials of anti-PD-1/PD-L1 agents

Author [year]	Phase of study	Study treatment	No. of patients	ORR (%)	Median PFS (months)	Median OS (months)	No. of patients with severe irAEs
Giaccone <i>et al.</i> [2018] (12)	II	Pembrolizumab	40 TC	22.5	4.2	24.9	6 (15%) patients
Cho <i>et al.</i> [2017] (13)	II	Pembrolizumab	26 TC, 7 T	24.2	6.2	NA (data not mature)	8 (24.2%) patients (5 T, 3 TC)
Rajan <i>et al.</i> [2017] (14)	I	Avelumab	7 T, 1 TC	25.0	NA	NA	5 (62.5%) patients

irAEs, immune-related adverse events; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T, thymoma; TC, thymic carcinoma.

Table 2 Ongoing clinical trials of anti-PD-1/PD-L1 agents

Study treatment	Tumor type(s)	Institution(s)	NCT number
Pembrolizumab + epacadostat	Thymic carcinoma	Georgetown University	NCT02364076
Pembrolizumab + sunitinib	Thymic carcinoma	Ohio State University Comprehensive Cancer Center	NCT03463460
Pembrolizumab	Thymic carcinoma, thymoma	M.D. Anderson Cancer Center	NCT03295227
Nivolumab	Thymic carcinoma, B3 thymoma	European Organization for Research and Treatment of Cancer (EORTC)	NCT03134118
Avelumab	Thymic carcinoma, thymoma	National Cancer Institute	NCT03076554

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors Mirella Marino and Brett W. Carter for the series “Dedicated to the 8th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2017)” published in *Mediastinum*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/med.2018.04.05>). The series “Dedicated to the 8th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2017)” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/med.2018.04.05

Cite this article as: Kim C, Giaccone G. The role of immune checkpoint blockade for treatment of thymic epithelial tumors—a delicate balance between efficacy and side effects. *Mediastinum* 2018;2:39.