Editorial Commentary

Evidence for treatment with anti-PD-1 antibody for thymic cancer: how to identify patients most likely to benefit

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Comment on: Giaccone G, Kim C, Thompson J, *et al.* Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol 2018;19:347-55.

Received: 21 September 2019; Accepted: 08 October 2019; Published: 26 November 2019.
doi: 10.21037/shc.2019.10.02
View this article at: http://dx.doi.org/10.21037/shc.2019.10.02

Thymic epithelial tumor (TET) is a rare disease with an annual incidence of 0.15 cases per 100,000 people (1). Accordingly, thymic carcinoma (TC) accounts for approximately 14% of all such cases (2). However, developing treatments for TC is fraught with many practical challenges, whereas critical medical needs remain unmet. Owing to the characteristics of the anatomical origin of the disease, a high incidence of immune-related adverse events (irAEs) associated with PD-1/PD-L1 antibodies has been reported. Given that TET is pathologically characterized by abundant intratumoral lymphocytes, inducing lymphocyte antitumor immunity has been considered to produce an antitumor effect (3). Considering the markedly longer progression-free survival (PFS) among patients with complete and partial responses, the development of treatments involving PD-1/PD-L1 antibodies has been of substantial importance. However, as TC is a rare disease, it is difficult to conduct randomized clinical trials. To date, two single-arm phase II trials for pembrolizumab and nivolumab in patients with TC and one single-arm phase II trial for pembrolizumab in patients with TET have been reported (4-6). In the trial involving nivolumab, none of the patients responded to treatment. Conversely, the trials involving pembrolizumab revealed a response rate of 19.2–22.5% with a median PFS of 4.2–6.1 months and a median overall survival of 14.5–24.9 months, indicating relatively good results. However, a comparison of the results obtained from clinical trials showed that it is unclear whether PD-1/PD-L1 antibodies are more beneficial than cytotoxic chemotherapy or molecular targeting drugs in unselected patients with TC/TET (7-9). Furthermore, because irAEs, including severe myositis and myasthenia, occurred in approximately 15–19.2% of the patients, effective predictive biomarkers are needed.

Predictive biomarkers already in clinical use for PD-1/PD-L1 antibody treatment include the tumor expression of PD-L1, tumor mutation burden (TMB), microsatellite instability (MSI), and tumor infiltrating lymphocytes (TILs). PD-L1 expression has been observed in 23–41% of patients with TC (10,11). Interestingly, PD-L1 glycosylation is important for its functioning, although glycosylated PD-L1 has not been recognized in current antibodies (12). Moreover, PD-L1 expression could be evaluated with greater accuracy by eliminating the N-linked glycosylation of PD-L1 in patient specimens via enzymatic treatment (13). Prioritizing such findings for the prediction of anti-PD-1/PD-L1 treatment efficacy may lead to considerable improvements in future patient selection. TC has been considered to have a lower TMB than other carcinomas; a few reports on MSI exist, with only one report indicating an incidence of 10% (1/10) for MSI (14). Regarding genetic mutation, the evaluation of insertion-deletion (indels) may become important (15). Several important reports have also been published regarding innate immune signaling. In *KRAS*; *LKB1* mutant non-small-cell lung cancer (NSCLC), the stimulator of interferon genes (STING) has received

attention as an important molecule that induces several T cell-produced chemokines. STING methylation is associated with low PD-L1 expression, making PD-1/PD-L1 treatment refractory (16,17). Giaccone *et al*. reported an extremely interesting clinical correlation between the expression of IFNγ-related genes and sensitivity to pembrolizumab (4). Thus, confirming the correlation between innate immune cytokine/chemokine production and clinical outcome has become important for PD-1/PD-L1 treatment. Although PD-1-positive TILs have been reported to serve as a prognostic marker for TC, standardizing such findings for clinical application has been difficult (18,19). Furthermore, despite the importance of developing biomarkers for identifying patients who develop irAEs, only few studies have reported such biomarkers. Patients with high-risk human leukocyte antigen (HLA), and thus a genetic predisposition for type 1 diabetes mellitus, have an increased risk for the development of immune checkpoint inhibitor-induced diabetes mellitus (20). Another interesting study reports that certain characteristics about symbiotic gut microbiota are associated with increased susceptibility to developing immune checkpoint inhibitor-induced enterocolitis (21). With regard to myocarditis, which is reported to be a severe adverse event in phase II trial in TC, the risk factors are not well understood (22). It is often difficult to distinguish TC from thymoma. Previous clinical trials may include thymoma patients who are thought to have a higher incidence of irAEs. The research for biomarkers that distinguish TC from thymoma may reduce the probability of irAEs in TC. In addition, the development of PD-1/PD-L1 antibody treatments for TC will require research to determine whether factors, such as PD-L1, TMB (MSI, indels), TILs, and innate immune signaling, are associated with clinical outcomes.

Although relatively good outcomes have been reported regarding pembrolizumab treatment in patients with TC, no report has investigated combination therapies. Studies have shown that an increase in the tumor mass increases CD8 T cells (Tex cells) exhaustion, thereby reducing the therapeutic effect of PD-1/PD-L1 antibody (23). This report supports the results of some clinical trials, which indicate that patients with a small tumor mass and those receiving early-line treatments tended to have better outcomes. The same report also suggests that combined therapy is promising considering that antigen presentation increases as the tumor mass decreases, indicating the importance of such clinical development. Studies on TC have shown that the survival benefit of adriamycin/cisplatin/vincristine/cyclophosphamide (ADOC) and carboplatin/paclitaxel (CBDCA + PTX) were comparable (24). However, CBDCA+PTX can be considered a better candidate for convenience. Furthermore, the inhibition of vascular endothelial growth factor (VEGF) axis can potentially reverse VEGF-induced immune suppression (25). Clinical trials are ongoing for sunitinib and vorolanib, which are receptor tyrosine kinase inhibitors. Moreover, combination therapy with radiotherapy has been considered a promising method for inducing abscopal effects (26). Nonetheless, the high incidence of irAEs (15%) has been one of the most important problems of PD-1/PD-L1 antibody treatment for TC. Therefore, to prolong the survival of patients with TC, it is important to identify biomarkers for patients expected to have high response rates and those likely to develop irAEs while further developing combination therapies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dr. Xiaomin Niu (Department of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: Takehito Shukuya: Research funding from: MSD; Personal fees from: MSD, AstraZeneca, Chugai, Eli Lilly, Ono Pharmaceutical. Kentaro Suina has no 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/shc.2019.10.02

Cite this article as: Suina K, Shukuya T. Evidence for treatment with anti-PD-1 antibody for thymic cancer: how to identify patients most likely to benefit. Shanghai Chest 2019;3:63.