Editorial

Uncommon efforts for an uncommon tumor: the case for development of newer systemic therapies for advanced thymic epithelial tumors

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Comment on: Merveilleux du Vignaux C, Maury JM, Girard N. Novel Agents in the Treatment of Thymic Malignancies. Curr Treat Options Oncol 2017;18:52.

Received: 27 November 2017; Accepted: 01 March 2018; Published: 13 March 2018.

doi: 10.21037/med.2018.03.04

View this article at: http://dx.doi.org/10.21037/med.2018.03.04

Thymic epithelial tumors (TETs) are a family of rare cancers that exhibit diverse histology and variable clinical behavior. The prognosis associated with TETs, especially thymomas, is generally good relative to other solid tumors with 5-year survival rates of 67% to 93% in patients with locally advanced disease that can be completely resected (1). However, up to 45% patients with World Health Organization subtype B3 thymoma and 80% of thymic carcinomas are locally advanced or metastatic at presentation and many of these patients are likely to have unresectable disease (2). Inoperable TETs are difficult to manage and are associated with a poorer prognosis (5-year survival rates of 36% for inoperable thymoma and 24% for inoperable thymic carcinoma) (1). Platinum-based chemotherapy is used to treat advanced, inoperable TETs. Patients with thymoma generally respond to treatment with objective response rates of 50% or more whereas approximately 20% patients with thymic carcinoma are expected to develop an objective response (3-5). Recurrent or refractory TETs have traditionally been treated with single-agent chemotherapy using drugs such as pemetrexed, gemcitabine, 5-fluorouracil, taxanes and ifosfamide (5). Response rates are lower and survival benefits are modest, especially for patients with thymic carcinoma. The lack of effective systemic treatment options for advanced and recurrent TETs has prompted the investigation of many novel drugs to overcome this unmet need. Merveilleux du Vignaux *et al.* have performed a comprehensive review of novel agents under development for treatment of TETs (6).

The first step in the rational development of targeted therapies is the identification of molecular alterations in a given tumor. As pointed out by Merveilleux du Vignaux and colleagues this is a challenge in TETs given the rarity and heterogeneity of these tumors. Despite these limitations, various groups including The Cancer Genome Atlas Research Network have successfully characterized genomic and epigenetic alterations in TETs and shown that these tumors have a very low mutational burden and few targetable genomic alterations (7-10). These observations provide an explanation for the lack of success of targeted biologic therapies, with a few notable exceptions (11). Sunitinib, a multikinase inhibitor which targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and KIT among other targets, and everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), induce objective responses in approximately one in four patients with thymic carcinoma (12,13). However, it should be noted that response to these drugs appears to be independent of mutations in KIT, PDGFR or components of the PI3K/AKT/mTOR signaling pathway. Similarly, as pointed out by Merveilleux du Vignaux *et al.*, KIT-mutant thymic carcinoma is not uniformly sensitive to KIT inhibitors such as imatinib. Therefore, actionable mutations when present in TETs, might not serve as reliable biomarkers to predict response to corresponding targeted therapies. The identification of predictive biomarkers of response should form an integral part of clinical trials evaluating targeted

therapies in TETs.

The rarity of TETs and the relatively poor predictive value of genomic abnormalities as described above, highlight the need to use innovative strategies to identify biologic therapies for further evaluation in patients with thymoma and thymic carcinoma. One approach is to identify potentially active drugs from phase I trials in which patients with TETs achieved response or durable stability (14,15). Indeed phase II trials of everolimus, the histone deacetylase inhibitor, belinostat, and the cyclin-dependent kinase inhibitor, milciclib, were initiated for patients with TETs based on evidence of activity in prior phase I trials.

Immune checkpoint inhibitors targeting programed death-1 (PD-1) or its ligand (PD-L1) have changed the landscape of treatment options for patients with advanced, unresectable cancers. These drugs have shown the ability to induce long-lasting responses and treatment is generally safe and well tolerated (16,17). PD-L1 expression is one of the determinants of response to PD-1/PD-L1 inhibitors. Merveilleux du Vignaux and colleagues have summarized studies assessing PD-L1 expression in TETs. These studies provide a rationale for evaluation of PD-1/PD-L1-directed immune checkpoint inhibitors in TETs. Our group and others have evaluated anti-PD-1/PD-L1 antibodies in patients with TETs and shown clinical activity accompanied by a high incidence of immune-related adverse events, especially in patients with thymoma (18-20). The incidence of treatment-related myositis, myocarditis and neuromuscular junction disorders has been observed to be much higher in patients with TETs treated with immune checkpoint inhibitors compared with other tumors. We have also observed development of delayed immune-related adverse events, often preceded by unrelated infections, several months after discontinuation of immunotherapy (unpublished data). These observations highlight the peculiar challenges associated with immune checkpoint inhibitor therapy in patients with TETs, and for these reasons we strongly discourage the use of immune checkpoint inhibitors in patients with TETs, especially thymomas, outside of a clinical trial.

In view of the limitations associated with currently available targeted therapies and immunotherapy for patients with TETs, there is a need for ongoing efforts to identify newer targets for treatment of these tumors. Merveilleux du Vignaux *et al.* highlight some of the impressive efforts made in this direction such as the establishment of programs like RYTHMIC and SPECTA-lung. Newer clinical trials are also available now based on the identification of novel targets such as the cell surface glycoprotein, mesothelin (21).

An emphasis on collaborations, as illustrated by the efforts of the International Thymic Malignancies Interest Group (ITMIG) is key to the development of newer drugs for advanced TETs, identification of prognostic and predictive biomarkers, and in overcoming the inherent challenges associated with research involving rare cancers.

Acknowledgments

*Funding:*This research was supported in part by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Yun Che (Cancer Hospital of Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/med.2018.03.04). The authors have 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/med.2018.03.04
Cite this article as: Achhal El Kadmiri MA, Rajan A. Uncommon efforts for an uncommon tumor: the case for development of newer systemic therapies for advanced thymic epithelial tumors. Mediastinum 2018;2:12.

