Editorial

Treatment of thymic malignancies—the way forward

Yesim Gökmen-Polar

Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Correspondence to: Yesim Gökmen-Polar, PhD. Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, 635 Barnhill Dr., MS-A128, Indianapolis, IN 46202, USA. Email: ypolar@iu.edu.

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Therapies for thymic malignancies

Epithelial tumors arising from the thymus gland are classified as thymomas and thymic carcinomas based on the histological classification of the World Health Organization (WHO) and staged using the Masaoka-Koga system (1-3). Thymic carcinomas are more aggressive neoplasms than thymomas and associated with early recurrence and metastasis leading to significant morbidity and mortality. As thymic carcinomas are frequently associated with higher tumor stage at diagnosis, a combination strategy including surgery, radiation and chemotherapy is prescribed for these patients. Many thymomas, on the other hand, are indolent tumors and it is necessary to have long term follow-up in order to make critical observations regarding their metastatic potential. One of the major steps in the definition of these malignancies is the fact that all thymic tumors (including type A thymomas) are malignant neoplasms (4,5). More recently, variants of type A tumors that have greater metastatic potential have been identified (6,7).

Merveilleux du Vignaux *et al.* (8) have provided a recent comprehensive review of the treatments for thymic malignancies. They highlight the point that many of the "hallmarks of cancer" are now being addressed by the treatments being used. To make a case for targeted therapies, the authors focus on the success of Everolimus, an mTOR inhibitor. In a clinical trial of 35 patients with thymoma and thymic carcinoma, there was 1 complete remission, 3 partial remissions and 21 patients with stable disease. Similarly, KIT activating mutations in thymic carcinomas have been targeted. There are a number of reports of the use of KIT inhibitors in thymic carcinomas leading to responses. The most successful targeted therapy is somatostatin analogues in octreoscan-positive thymomas. In an ECOG trial of 38 octreoscan-positive patients, response was noted in 12 patients with 1-year survival of 87% in response to a sequential combination of octreotide and prednisone.

The authors have also discussed a number of novel agents in thymic malignancies. These include the PI3 kinase inhibitors, cyclin-dependent kinase (CDK) inhibitors, anti-angiogenesis inhibitors as well as multi-kinase inhibitors (e.g., sunitinib). These have all some activity. The histone deacetylase inhibitors are of particular interest in these groups, as we have previously shown that there is a genetic abnormality in this pathway in many thymomas (9).

The recent interest in the use of immune checkpoint inhibitors has resulted in trial of these agents in thymic tumors. Thymomas are good candidates for these forms of therapy, as number of studies have documented PD-1/PDL-1 expression in these tumors. These trials have shown significant promise albeit associated with significant toxicities. Merveilleux du Vignaux *et al.* recommend that these agents should be used outside the context of clinical trials only after careful consideration and expert consultations.

Barriers to targeted therapies

Major handicaps to the rational development of therapies include the rarity of thymic tumors, the indolent behavior of many tumors and lack of good model systems. Some groups including ours have sought to address the issue of models by developing cell lines and animal models (10,11), but these are still imperfect representation of the disease states. The

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understanding of thymic epithelial tumors has significantly changed within the last decade. Two processes underpin this change- the availability of large cohorts of thymic tumors and the better elucidation of the molecular processes.

The establishment of a virtual tissue bank by the International Thymic Malignancy Interest Group (ITMIG) has resulted in a dramatic increase in knowledge of thymic tumors (12); this will be a gift that keeps on giving in the years to come. More specifically, it will enable a detailed cataloguing of the time to recurrence and patterns of recurrences. The long tumor dormancy is another major issue. While it has been established that thymic carcinomas are more aggressive neoplasms than thymomas, most clinical trials have combined these tumors in their study design. Recurrence rates defer dramatically even within thymomas. Our group has sought to establish a gene signature to identify the patients who are most likely to recur (13). This was licensed out to Castle Biosciences (Decision Dx thymomas) but the lack of clinical interest in using this assay has resulted it being no longer offered commercially. Assays such as these, particularly if used in the context of a clinical trial, will offer insights in response to therapies.

The Cancer Genome Atlas (TCGA) analysis of thymic tumors could contribute to understanding the molecular basis of these tumors (14). Fortunately or unfortunately, thymomas are associated with low mutation frequency and the little is known about the gene (*GTF2i*) in which mutations are most common (14,15). The TCGA analysis has identified 4-classes of thymomas, additional studies are necessary to clarify if these sub-groups have therapeutic relevance. Of note, the Decision Dx thymoma signature clearly identified the recurrent tumors in this dataset (unpublished data).

The treatment of thymic tumors has yet to evolve and incorporate these new anatomic and molecular findings. The treatments have been largely based on a broad histological classification (thymoma and thymic carcinoma) and anatomic parameters such as tumor size, involvement of adjacent structures and amount of residual disease after surgery. Neoadjuvant therapies have been successfully used to decrease the tumor size and permit tumor resection. The post-surgical therapies are based largely on experience in other cancers such as lung cancer. One of the major caveats in determining therapeutic efficacy is the fact that many thymic tumors are composed of a significant component of lymphocytes; these might be dramatically reduced by chemo- and radio-therapy giving a misleading impression of response to treatment. Additionally, the involvement of the pleura is difficult to evaluate and confirm therapy response.

Conclusions

Thymic tumors continue to remain an enigma. The development of ITMIG is clearly an important landmark that will lead to improved understanding of these tumors. The RYTHMIC (*Reseau tumeurs THYMiques et Cancer)* in France has been developed as a cooperative group for the management of patients with thymic tumors. These good initiatives deserve support. There is an acute need for a multi-disciplinary, multi-institutional, multi-national approach for the development of evidence based therapies of thymic tumors that take in to account the complex histological features, gene expression and mutation patterns and the heterogeneity in the natural history of disease.

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Footnote

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