"Hot topics" in thymic epithelial tumors: a special series from the ITMIG 2019 annual meeting

It is a pleasure to present in updated version the contributes of this Special Series including the Lectures at the last Annual meeting held in presence at Niagara on the Lake in October 2019 by the world-wide International Thymic Malignancy Interest Group (ITMIG) community. This special series from the journal "*Mediastinum*" presents now the expanded and updated lectures. The difficult period prevented from having all the Lectures here. However, the reader will find a comprehensive exposition of most of the "hot topics" in thymic epithelial tumors (TET).

In the first paper, Meinoshin Okumura reports on the Japanese community of TET healthcare professionals. In Japan several scientific societies exist engaged in the study and treatment of TET. In particular, the Japanese Association for Research of the Thymus (JART) is a cross-sectional association of physicians and researchers engaged in thoracic surgery, medical oncology, neurology, radiology, pathology. Among the accomplishments of this scientific society, JART also contributed actively to establish, in collaboration with ITMIG and IASLC, the first official UICC TNM staging system for TET. A further society, the Japanese Joint Committee for Lung Cancer Registry (JJCLCR), has established a national database of lung cancer, thymic epithelial tumor, and malignant mesothelioma cases. Moreover, because of the new, increasing needs, at present JART and JJCLCR are building a joint prospective database of TET cases.

Similarly, in the second paper, Dong Kwam Kim describes the organization and the activities of the KART, Korean Association for Research on Thymus. This society was built due to the joint activity of the four hospitals in Korea treating the higher amount of surgical cases of TET. Basing on the ITMIG database, also KART established a multicenter TET database, aimed to collect data both retrospectively and prospectively, in order to analyze the clinical features and treatment outcomes in Korea. Moreover, the database is expected to provide data useful to establish, in collaboration with ITMIG, guidelines and standards for TET's treatment.

In his review on the surgical approach to TET, Shaf Keshavjee reviews the treatment strategy for locally invasive, advanced, and metastatic TET. The purpose, in all risk appropriate patients, is to reach by surgery an R0 resection status. Multimodal therapies are expected to be beneficial for patients particularly with locally advanced disease. Neoadjuvant therapies may increase the likelihood to reach an R0 resection status.

In his review, Anthony Brade summarizes and discuss the current literature regarding radiotherapy indications and explores issues surrounding radiotherapy (dose-response-relationships) for thymomas and thymic carcinoma. In the case that complete resection of TET is not feasible the author discuss the use of post-operative radiotherapy (PORT) to improve local control. Currently, NCCN guidelines suggest a PORT dose range of 45–50 gray (Gy) for completely resected disease (R0), 54 Gy for patients with microscopic residual disease (R1) and 60–70 Gy for patients with gross residual disease (R2). However, these recommendations still need convincing evidences. The author provides an initial rationale for the use of radiotherapy in thymoma and in thymic carcinoma. However, only long-term prospective studies, based on image-guided radiotherapy and modern surgical techniques, will allow to define the optimal radiation therapy in TET.

Sukhmani Padda presents and discusses in her paper the treatment strategies for advanced TET. A neoadjuvant setting in fact is advisable, due to the chemosensitivity and radiosensitivity of TET. This approach could reduce the tumor burden and improve the likelihood of achieving a complete resection. S. Padda summarizes the existing literature on the role of induction therapy for advanced thymic malignancies and emphasizes the role of the expert multidisciplinary tumor board in the selection of appropriate candidates.

The role of immunotherapy in TET is explored by Arun Rajan in his paper. Among TET, in fact, autoimmune paraneoplastic diseases are frequent, especially in thymomas. The defects in immunological self-tolerance represent unique biological characteristics often associated to these tumors. Adopting immunotherapy in TET patients brings to an increased risk of severe immune-mediated adverse events. Therefore, it is crucial to identify patients at low risk for development of severe immune toxicity and who might benefit from treatment. On one hand, the discovery of novel biomarkers of response and toxicity is particularly important. On the other side, prospective clinical trials, including trials of immune checkpoint inhibitors, include or should include the evaluation of risk mitigation strategies.

Finally, Claire Merveilleux du Vignaux and Nicolas Girard discuss the requisites of appropriate clinical trials. TET in fact due to their biological characteristics (rarity of cases, long survival also after multiple relapses, difficulties in establishing good landmarks and wise endpoints, lack of biomarkers) represent a real challenge in order to set up valuable clinical trials. A good selection of patients, the identification of adequate endpoints, the integration of well-defined biomarkers is crucial to the building up of trials fulfilling the clinical needs. Targeted therapies, to be effective, need the identification of distinct TET molecular subgroups, and several projects currently focus on this goal. Among them, the European SPECTA, an EORTC project (https://www.eortc.org/specta/) in conjunction with EURACAN, is currently in progress to get a better understanding of the genomic landscape of rare diseases and, among rare tumors, of TET.

Last but not least, two case reports, one by Malgorzata Szolkowska and one by Anja C. Roden bring us on a real-life diagnostic work-up. In her case report, Malgorzata Szolkowska describes an unusual thymic mass with both features of thymoma of undefinied histological type and of thymolipoma. Arguments for and against both types of tumors were presented, but the final diagnosis was not reached, even after an extensive discussion among several expert pathologists during the 2019 ITMIG Annual Meeting. It was impossible to establish unequivocally the biological character of the tumor and to make a clear distinction between an unusual thymoma and a thymolipoma-like lesion. The clinical outcome will be decisive, providing arguments to support one or the other diagnosis.

In the last report, Anja C. Roden reports on a thoracic SMARCA4-deficient undifferentiated tumor (SMARCA4-UT), an aggressive poorly differentiated epithelioid thoracic tumor, usually metastatic when first detected, that most commonly occur in the mediastinum of male smokers. These tumors, due to an inactivating mutation of SMARCA4, show a loss of expression of the brahma-related gene 1 (BRG1); moreover, they show no or only focal keratin expression. It is unclear if these tumors represent de-differentiated lung adenocarcinomas or might be related to BAF-deficient rhabdoid tumors. However, the correct diagnosis is important as preclinical and early clinical trials using enhancer of zeste homolog (EZH2) inhibitors are promising.

Taken together, the papers of the Special Series of "*Mediastinum*" devoted to the 10th Annual ITMIG meeting present and discuss the "hot topics" in TET evaluation and treatment, show the relevance of national/international networking and the necessity of national/international adequate database establishment. At the same time, the papers and reviews submitted demonstrate that the wide pathological/biological spectrum of TET and of other rare mediastinal tumors and their oncological behavior are still far to be extensively explored.

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