Mini-Review

Use of immune checkpoint inhibitors in thymic epithelial tumors

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Abstract: Thymic malignancies represent a heterogeneous group of rare thoracic cancers, which may be aggressive and difficult to treat. Thymic carcinomas are more aggressive tumours with frequent metastatic spread to lymph nodes and distant sites. In this setting, the use of immune checkpoint inhibitors has been considered a potential strategy for the treatment of those tumors. Overall, while immune checkpoint inhibitors targeting PD-1 or PD-L1 show promising efficacy, with response rates and duration of response in line with reported studies in other solid tumours, toxicity remains a major concern, despite systematic baseline workup for autoimmunity, with frequent occurrence of severe auto-immune adverse events. Therefore, immunotherapy is currently not a standard-of-care in thymic epithelial tumors, and should be further studied in clinical trials.

Keywords: Immunotherapy; PD-1; thymoma; thymic carcinoma

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Thymic malignancies represent a heterogeneous group of rare thoracic cancers, which may be aggressive and difficult to treat. Thymic epithelial tumours are classified according to the World Health Organization system that distinguishes thymomas from thymic carcinomas; while thymomas are usually slow-growing tumours with a tendency towards local and regional invasion, thymic carcinomas are more aggressive tumours with frequent metastatic spread to lymph nodes and distant sites (1). In this setting, the use of immune checkpoint inhibitors has been considered a potential strategy for the treatment of those tumors.

Auto-immunity in the thymus and in thymomas

The thymus physiological role is to induce central tolerance to self-antigens, through the control of the differentiation and the subsequent positive and negative selection of immature T cells (2). This process is being deregulated along with thymic carcinogenesis: (I) immature thymoma-derived lymphocytes may escape the disorganized tumour environment without passage through the thymic medulla where self-tolerance is induced; (II) medullary thymic epithelial cells present with defects regarding their unique capability to express tissue-related antigens, related to a loss of expression of the transcription factor AIRE (Autoimmune Regulator), similar to what is described in APECED (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy); (III) thymic carcinogenesis may be associated with genetic changes that impair the development of T-cells, and generate an increased number of self-reactive lymphocytes.

Auto-immune disorders are a clinical hallmark of thymomas

One third of patients diagnosed with thymoma present at the time of diagnosis, with autoimmune disorders, the most frequent being myasthenia gravis (3). Other frequent disorders include pure red cell aplasia (5% of cases), and hypogammaglobulinaemia (5% of cases). Those disorders are then not paraneoplastic syndromes, which would recover after resection of the tumour; as they are rather related to self-reacting lymphocytes than escaped from negative selection in the thymus, those auto-immune diseases usually

have a course that is independent from the evolution of the tumour.

Systematic immunological check-up is recommended when a diagnosis of thymic epithelial tumour is suspected (1); auto-immune disorders, even if latent at the time of diagnosis, may significantly impact any therapeutic intervention, including surgery, radiotherapy, chemotherapy, and even more immunotherapy, with a risk of acute exacerbation. Auto-immune disorders are not observed in thymic carcinomas, which still may be associated with true paraneoplastic syndromes related to the direct secretion of cytokines or hormones by tumour cells.

PD-L1 expression in the thymus and in thymic epithelial tumours

PD-L1 expression, while being observed in more than 90% of epithelial cells of the normal thymus with a medullar tropism respecting Hassall's corpuscles, was also identified in thymomas and thymic carcinomas using various immunohistochemistry protocols (4-6). The significance of this finding as a rationale for the assessment of immune checkpoint inhibitors targeting PD-1 or PD-L1 remains debatable, given (I) the high frequency of PD-1 and PD-L1 expression in the non-neoplastic thymus, (II) the fact that in thymomas, the presence of immature and mature T cells surrounding tumour cells is part of the prototypic architecture, and not a marker of actual antitumour response, (III) the potential immune modulation induced by chemotherapy or targeted agents, such as reported with sunitinib, which are part of standard treatment strategy in advanced disease, and may lead to modulate PD-L1 expression in immune cell populations including Tregs.

Clinical results with PD-1 and PD-L1 immune checkpoint inhibitors

One phase II trial was conducted with pembrolizumab, a fully humanized IgG4 Ab that targets the PD-1 receptor, in patients with advanced, refractory thymic carcinomas (NCT02364076) (7). In this study, any history of autoimmune disease or other malignancy requiring treatment were exclusion criteria. Pembrolizumab was given at 200 mg every 3 weeks. Out of 41 patients, 6 (15%) developed serious autoimmune disorders: 2 cases of polymyositis and myocarditis, with complete recovery with steroids but requirement of pacemaker for complete auriculo-ventricular block; one case of pancreatitis, hepatitis, and diabetes mellitus type 1; one case of bullous pemphigoid, recovering with steroids; 1 case of polymyositis and hepatitis; and 1 case of transaminitis; 3 patients had to discontinue treatment after one of those adverse events. Response rate was 23%: there were 1 complete response, 8 partial responses, and 21 (53%) patients with stable disease; median duration of response was 23 months. Median progression-free and overall survival were 4.2 and 24.9 months, respectively. PD-L1 expression—using immunohistochemistry with DAKO 22C3 antibody—was observed in ≥50% of tumour cells for 10 patients, 6 of whom had response to pembrolizumab; only 3 patients of the 27 patients with PD-L1 expression by tumour cells <50%, had response. A similar trial was conducted in Korea (NCT02607631). This phase II trial enrolled 26 patients with thymic carcinoma, and 7 patients with thymoma, and results were presented at ASCO 2017 Annual Meeting (8). Response and stable disease rates were 24% and 55% respectively, with progression-free survival ranging from 6.1 to 9.0 months, respectively. Treatment-related adverse events ≥ grade 3 associated with immune related adverse events (irAE) included hepatitis (4 cases), myocarditis (3 cases), myasthenia gravis (2 cases), thyroiditis (1 case), ANCA-associated rapidly progressive glomerulonephritis (1 case), colitis (1 case), and subacute myoclonus (1 cases); despite management with high dose corticosteroid and other immunosuppressive agents, 8 patients discontinued study treatment.

Overall, while immune checkpoint inhibitors targeting PD-1 or PD-L1 show promising efficacy in thymic carcinomas, with response rates and duration of response in line with reported studies in other solid tumours, toxicity remains a major concern, despite systematic baseline workup for autoimmunity, with frequent occurrence of severe auto-immune adverse events, still possibly favored by previous treatments with anthracyclins and radiation therapy. Therefore, immunotherapy is currently not a standard-of-care in thymic epithelial tumors, and should even not be delivered in an off-label setting, especially if the patient is eligible for ongoing clinical trials. In Europe, the European Organization for Research and Treatment of Cancer (EORTC) and the European Thoracic Oncology Platform (ETOP) are now starting a single-arm, multicentre, phase II study—the NIVOTHYM trial—to assess the efficacy of nivolumab alone or combined with ipilimumab in patients with advanced, refractory type B3 thymomas and thymic carcinomas; a strict autoimmune workup is planned (NCT03134118). A phase I/II trial with pembrolizumab in

thymic carcinoma and thymoma is also being initiated at MD Anderson Cancer Center (NCT03295227).

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Footnote

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