BRIEF REPORT

Immune Checkpoint Inhibitors for the Therapy of Thymoma

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Introduction

We present the case of a healthy 39-year-old woman who, in the context of a presternal chest pain, underwent a thoracic computed tomography (CT) scan in September 2016, in which an anterior mediastinal mass of 11 cm × 6 cm × 12 cm was found in contact with the superior vena cava, ascending aorta, trunk of the pulmonary artery, and pericardium. In addition, bilateral pleural effusion and subcarinal 12-mm adenopathy were described. Through positron emission tomography–CT, the mass with malignancy characteristics was confirmed, without evidence of distant disease. After a core needle biopsy with a pathologic result suggestive of thymoma, a median sternotomy with complete resection was performed, and a definitive anatomopathologic report revealed thymoma B1 (90%), Masaoka-Koga IIb grade with a compatible immunohistochemistry pattern (positive keratin 19, tumor protein p40, tumor protein p63, cluster of differentiation 3, rapid diagnostic test, and cluster of differentiation 1a). Furthermore, an extended immunohistochemical analysis revealed an anti–programmed death-ligand 1 (anti–PD-L1) antibody (clone 22C3) membrane immunoreactivity more than 50% of the tumor cells. In addition, a next-generation sequencing study (Oncomine focus assay) was performed, and no gene alteration was found. There was no evidence of lymph node involvement, but an infiltration of the capsule with mediastinal soft tissue extension and fibrous adherence to visceral pleura was described. An adjuvant treatment based on local radiotherapy (50 Gy) was performed.

In the follow-up, a body CT scan revealed a mediastinic, pleuropulmonary metastasis and liver relapse (disease-free survival, 10 mo). A neoadjuvant chemotherapy based on carboplatin, adriamycin, and cyclophosphamide was performed with a partial response on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1 criteria after three cycles, which required a dose modification owing to grade 3 hematologic toxicity, followed by an incomplete (affected margins) surgical resection. An adjuvant chemotherapy was then planned with five cycles of cisplatin and pemetrexed with a very poor tolerance (grade 3 gastrointestinal and hematologic toxicity) and was subsequently stopped.

During the follow-up, in September 2018, a positron emission tomography–CT scan was performed, which revealed a new secondary asymptomatic progression of the disease in the lymph node, pleura, and liver (progression-free survival [PFS], 9 mo). After the chemotherapy toxicity and the strong positive PD-L1 overexpression, we decided to start with immunotherapy after the

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scheduled dose of pembrolizumab 200 mg every 3 weeks. The tolerance treatment was excellent (only grade 1 fatigue, diarrhea, and dry skin), and a complete response on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1 criteria was described after 9 weeks and 18 weeks of the treatment (Fig. 1). Actually, the patient continued on the treatment with a maintained clinical and radiological complete response and no toxicity profile abnormalities (PFS, 18 mo).

Discussion: The Role of the Immune Checkpoint Inhibitors in Thymoma

Thymic epithelial neoplasms are rare tumors with an incidence of 1% in all adult cancers, but they are the most common types among the tumors of the anterior mediastinum. They are divided into thymomas and thymic carcinomas.[1,2] Thymomas are further subdivided into different types (so-called A, AB, B1, B2, and B3) on the basis of the relative proportion of the nontumoral lymphocytic component and the resemblance to normal thymic architecture.

The management of thymic epithelial neoplasms is a paradigm of multidisciplinary collaboration. Complete surgical resection is the only potentially curative option. For the metastatic disease, palliative chemotherapy based on platinum is the first-line standard therapy.[3] A few prospective studies have investigated multiple novel agents with variable outcomes. Alternative options have emerged, including targeted agents based on recent molecular data, antiangiogenics, and immune checkpoint inhibitors. Most data are related with thymic carcinomas.

Recently, a phase II study of sunitinib[4] revealed high antitumor activity with an overall response rate (ORR) of 26% in 23 pretreated patients with thymic carcinomas but only 6% in 16 pretreated patients with thymoma. Moreover, Giaccone et al.[5] reported that pembrolizumab in pretreated patients with thymic carcinomas (no thymoma population was included) resulted in an ORR of 22.5%, a median PFS of 4.2 months, and a marked correlation between high PD-L1 expression and better response. Nevertheless, 15% of the patients developed grade 3 to grade 4 immune-related adverse events (irAEs) such as myocarditis, hepatitis, myasthenia gravis, bullous pemphigoid, and type 1 diabetes mellitus.

A phase II Korean trial[2] included 33 patients, 26 with thymic carcinomas and seven with thymomas. All of the thymoma population had Eastern Cooperative Oncology Group grades 0 to 1, 28.6% had extrathoracic disease (pleura, lymph node, and pericardium were the most frequent metastatic sites), and 42.9% received three or more previous chemotherapy lines (no patient completed previous radiotherapy). All the patients received pembrolizumab intravenously at a fixed dose of 200 mg every 3 weeks until disease progression, death, or unacceptable toxicity up to 24 months. The primary end point ORR among the patients with thymoma was 28.6% (two patients had partial response and five had stable disease),

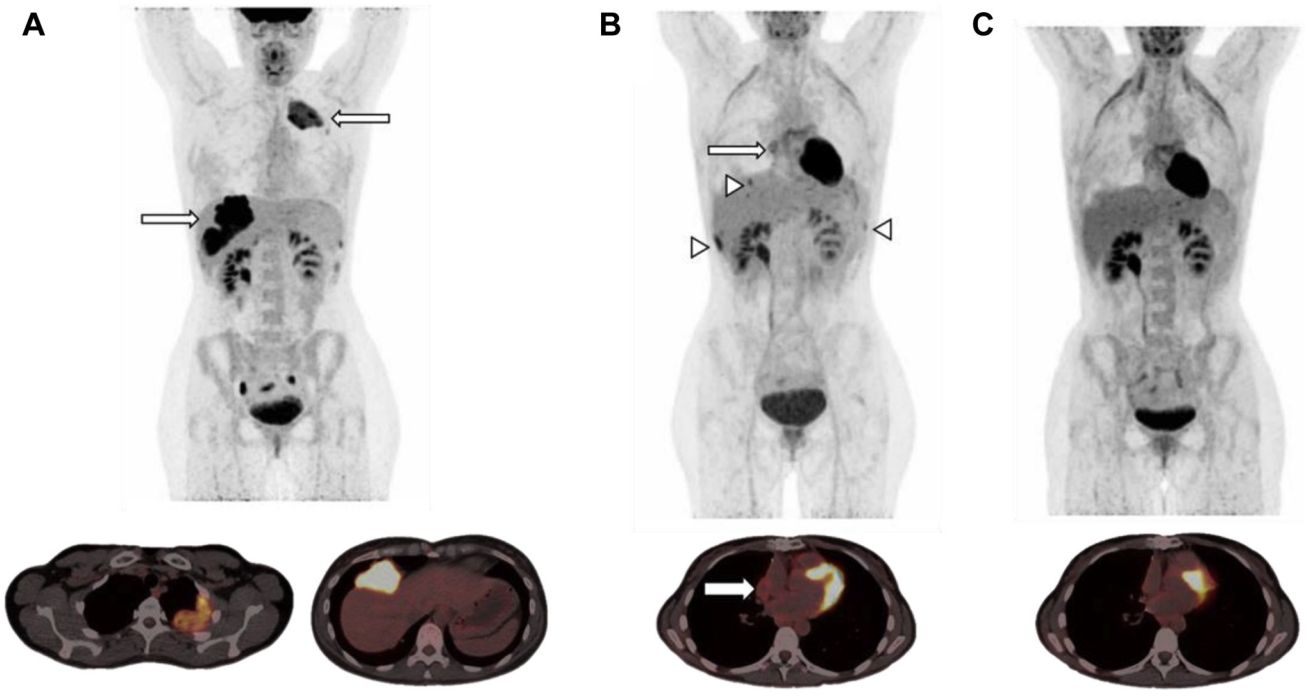

Figure 1. (*A*) Arrow: bilateral pleural metastases; (*B*) right preauricular mediastinal progression (arrow) and lymph node and pleural metastases (arrowhead); (*C*) positron emission tomography complete metabolic response.

which resulted in a disease control rate of 100%. The median duration of the response was not reached. Five of seven patients (71.4%) with thymoma had grade 3 to grade 4 irAEs, such as myocarditis (three, 42.9%), hepatitis (two, 28.6%), thyroiditis (one, 14.3%), colitis (one, 14.3%), conjunctivitis (one, 14.3%), and nephritis (one, 14.3%). Two of these patients who developed severe irAEs had a previous history of myasthenia gravis. Most of the patients experienced severe irAEs after the first or second cycle of pembrolizumab treatment: 87.5% of the patients who discontinued treatment fully recovered from the irAEs with the administration of high-dose corticosteroids and other immunosuppressive agents in a median time of 15 weeks. A strong correlation was found between high PD-L1 immunohistochemistry expression of greater than 50% tumor proportion score and partial response, whereas none of the patients with low PD-L1 expression had a response. However, there were no differences between PD-L1 expression and development of severe irAEs.

Finally, seven patients with thymoma and one patient with thymic carcinoma were enrolled in a phase I, dose-escalation trial of avelumab[6] at doses of 10 mg/kg to 20 mg/kg every 2 weeks until disease progression or development of intolerable side effects. Two of the seven patients with thymoma (29%) had a confirmed partial response, two (29%) had an unconfirmed partial response, and three (two with thymoma, one with thymic carcinoma) had stable disease (43%). All the responders developed irAEs that were resolved with immunosuppressive therapy. The responders had higher immune cell subset populations (higher absolute lymphocyte count, lower frequencies of B cells, regulatory T cells, conventional dendritic cells, and natural killer cells) before the therapy than the nonresponders.

Although most of the clinical studies with immune checkpoint inhibitors included a low number of patients with thymoma, the results regarding ORR and duration of response were encouraging in PD-L1 greater than 50% tumors. Nevertheless, given the relatively high incidence of irAEs, toxicity should be carefully monitored to detect and manage irAEs in the early period of treatment because these adverse events can be fatal.[7]

In conclusion, to our knowledge, this is the first case report of extended complete response to pembrolizumab (18 mo) in patients with heavy metastatic B1 thymoma PD-L1 greater than 50% with no severe irAEs.

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