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Case report

The clinical benefits of immune checkpoint inhibitor for thymic carcinomas ～experience of single public hospital in Japan～

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A B S T R A C T

Thymic carcinomas is rare and highly aggressive carcinoma. Most patients with them are diagnosed as being at surgically unresectable stages due to it. There are several reports which showed the effect of chemotherapy, however, it is controversial. Recently, immune checkpoint inhibitors have changed conventional chemotherapy due to their effect against various types of cancers. We administered nivolumab, anti-Programmed Cell Death (PD)-1 antibody, to four patients with unresectable thymic carcinomas who had previously undergone conventional chemotherapy. A histopathology on tumors from these patients revealed the presence of squamous cell carcinoma and PD-L1 high expression. After treatment with nivolumab, it seemed to be beneficial to all patients; The best clinical responses of 3 patients were partial response and that of the other one was stable disease. None of them experienced severe immune-related adverse events. Our results suggest the potential benefits of using these inhibitors to treat thymic carcinomas in real world clinical setting as is the cases in recent clinical trials for the evaluation of immune checkpoint inhibitors for the treatment of thymic carcinoma.

1. Introduction

Thymic carcinoma is a rare carcinoma which arises in the mediastinum. In most cases, thymic carcinoma is unresectable because it is highly aggressive and is usually found at an advanced stage [1]. In such cases, chemotherapy is indicated to the primary treatment, however, the effect of it has not been proven because it was rare carcinoma having difficulty to conduct clinical trials, which requires more effective modality.

Immune check point inhibitors have improved the treatment of tumor and the effect has been proved with various cancers including squamous none small cell lung cancer [2]. On the other hand, the evidence of an effect to thymic carcinoma is not enough. Recently, it was reported that thymic carcinoma showed high expression of PD-L1 as with other cancers [3], which indicates the potential benefits of nivolumab with thymic carcinomas and a phase 2 study of pembrolizumab in patients with thymic carcinomas was published [4]. We administered nivolumab to 4 patients with thymic carcinomas and evaluated the effect on the tumors.

2. Case presentation

2.1. Case 1

A 72-year old female was admitted to our hospital with edema because of superior vena cava syndrome (SVC syndrome) and after systemic evaluation in August 2017, she was diagnosed as having thymic carcinoma with pleural dissemination and metastasis of liver, cT4N2M1b, stage IVb. The systemic chemotherapy was performed with carboplatin (CBDCA) + nanoparticle albumin-bound paclitaxel (nab-PTX) as the first line regimen in September 2017. After 2 cycles of the regimen, Positron Emission Tomography-Computed Tomography (PET-CT) revealed stable disease.

The chemotherapy did provide the symptom relief of SVC syndrome, and we performed radiotherapy, 30 Gy in 10 fractions from November 2017 and was well responded to the symptoms. In December 2017, the patient began to receive the immunotherapy with nivolumab as a 2nd line regimen and after 5 cycles of it, radiological evaluation showed very well response to tumor in February 2018 (Fig. 1A and B).

2.2. Case 2

A 64-year old female was admitted to our hospital with the complain of dyspnea on exertion. Chest X-ray showed left pleural effusion and PET-CT revealed the accumulation of Fluoro-Deoxy-Glucos in the anterior mediastinal tumor, liver tumor and lymphadenopathy. After bronchoscopy biopsy, the patient was diagnosed as having thymic carcinoma, cT2N3M1b, stage IVb in September 2016. CBDCA and nab-PTX was selected as first line chemotherapy and after 4 cycles of it, nab-PTX could not be continued due to neutropenia with common

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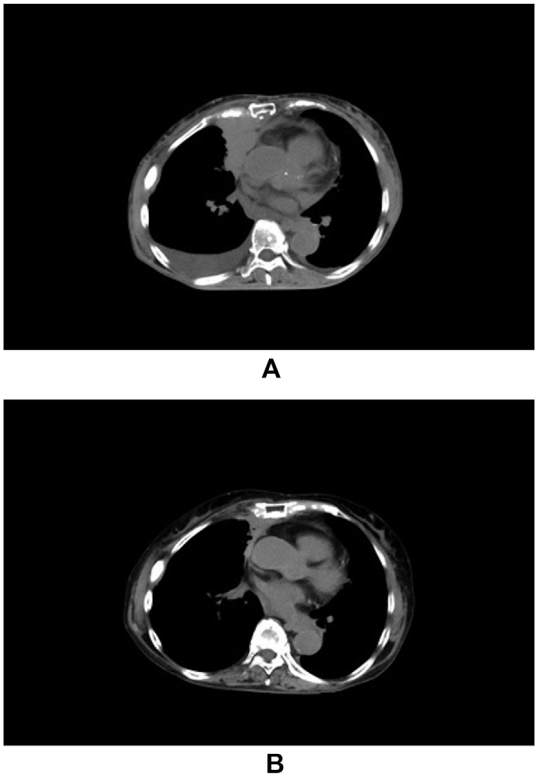

Fig. 1. Radiological change on CT after treatment of nivolumab in case 1. **A**. Chest CT at diagnosis which showed a large mass in mediastinal which disseminated to pericardium and right pleura. **B**. After treatment of nivolumab, the size of primary tumor in mediastinal was remarkably reduced and right pleural effusion almost disappeared.

terminology criteria for adverse events (CTCAE) version 4.0 grade 4. After another 2 cycles of CBDCA monotherapy, the tumor was considered to be progressive disease with PET-CT in March 2017 and the immunotherapy with nivolumab was performed as 2nd line regimen. After 4 cycles of nivolumab, the tumor was considered to be well responded to the treatment in the CT image and continued to become smaller now in December 2017.

2.3. Case 3

A 66-year old man with a past history of Hodgkin's lymphoma was admitted to our hospital for anterior mediastinal tumor, which was diagnosed as thymic carcinoma. Systemic evaluation indicated cT4N1M1b (pleural seeding), stage IVb in September 2010. CBDCA and PTX was administered as a first line chemotherapy, which revealed progressive disease after 4 cycles of its. We selected gemcitabine (GEM) monotherapy as a second line chemotherapy. Although best overall response of the GEM monotherapy showed partial response during 44 cycles over 4 years, the tumor was finally metastasized to cervical lymph in August 2017. The chemotherapy was changed to immunotherapy with nivolumab and after 4 cycles of it, radiological response revealed partial response, and after another 8 cycles of it, smaller tumor size remained at primary region, however metastatic region showed progressive disease in February 2018.

2.4. Case 4

A 72-year old female was admitted to our hospital with the shadow of right pulmonary hilar lesion in chest X-ray. CT-guided biopsy of the tumor showed thymic carcinoma and systemic evaluation diagnosed it as cT4N3M1 (multiple metastatic pulmonary tumor), stage IVb in February 2013. CBDCA and PTX was selected as a first line chemotherapy and after 5 cycles of it, progressive disease was revealed. The patient received 6 cycles of GEM as a second line chemotherapy, finally leading to stable disease. In March 2017, re-biopsy was performed, showing 1–49% expression of PD-1, and nivolumab was selected as a 3rd line chemotherapy. The patient could not continue to receive nivolumab after 6 cycles of it because of anorexia (CTCAE grade 3) and general malaise (CTCAE grade 3) and radiological evaluation showed stable disease now, January 2018.

3. Discussion

For thymic carcinoma, surgery is indicated as the initial treatment for patients who are considered to be feasible and complete surgical resection has been reported to be an important prognostic factor. However, previous studies showed that most thymic carcinoma have already invaded to mediastinal structures at the first diagnosis; A retrospective study identified 45% of the patients with thymic carcinomas had Masaoka stage III and 33% of the patients had stage IV [5]. In unresectable cases, chemotherapy is indicated as the primary treatment. Although any standard regimen has not been established, several regimens are acceptable in the real world clinical setting; For examples, combination therapy of cyclophosphamide, doxorubicin and cisplatin or combination therapy of cisplatin and etoposide are selected for thymic carcinomas [6]. It was noted that chemotherapy was associated with overall survival and progression free survival in some reports, however, a retrospective study conversely showed no benefit on the use of it, which means that the effect of conventional chemotherapies are controversial [5]. On the other hand, recently, immune checkpoint inhibitors have received remarkable attention for the therapy of several malignancies. Some retrospective studies showed PD-L1 expression with thymoma and thymic carcinoma was significantly correlated to pathological features and Masaoka stage [7]. The studies provided the potential activity of anti PD-1/PD-L1 medications for the treatment of thymus and thymic cancer.

We administered immunotherapy with nivolumab to 4 patients with unresectable thymic carcinoma as a second or third line regimen, whose characteristics are shown in Tables 1 and 2. All patients had histopathology of squamous cell carcinoma. They had received previous conventional chemotherapies, however, there were no sufficient response to them. All patients had positive PD-L1 expression in their tumor by 22C3 pharmDx kit staining. All patients showed well response to the immunotherapy with nivolumab; CT scan revealed the partial response of tumor in 3 patients and tumor biomarker was decreased in the other patient, especially in case 1, the size of tumor was remarkably

Table 1
Characteristics of patients with thymic carcinoma.

Case	Age	Sex	PD-L1 expression	Masaoka stage	Best clinical response
1	72	F	TPS 1–24%	cT4N2M1b stage IVb	PR
2	64	F	TPS > 50%	cT2N3M1b stage IVb	PR
3	66	M	TPS > 50%	cT4N1M0 stage IVa	PR
4	72	F	TPS 1–49%	cT4N3M1 stage IVb	SD

Abbreviation: F = female, M = male, Sq = squamous cell carcinoma, TPS = tumor proportion score, PR = partial response, SD = stable disease.

Table 2
Course of treatment.

Case	Prior chemotherapy
1	CBDCA + nab-PTX, RTX, Nivolumab
2	CBDCA + nab-PTX, nab-PTX, Nivolumab
3	CBDCA + PTX, GEM, Nivolumab
4	CBDCA + PTX, GEM, Nivolumab

Abbreviation: CBDCA = carboplatin, nab-PTX = nanoparticle albumin-bound paclitaxel, GEM = gemcitabine.

reduced. Recently, a phase 2 study of pembrolizumab in patients with thymic carcinomas was published, which showed pembrolizumab was a promising treatment option for thymic carcinoma [4].

According to a systematic review, higher PD-L1 expression in patients with non-small cell lung cancer are more likely to experience treatment benefits with anti PD-1/PD-L1 antibodies although there are a few studies which conversely showed the treatment benefits of these drugs were independent of tumor PD-L1 expression [8]. There was no previous report about the association between PD-L1 expression and benefits of immune check point inhibitors in thymic carcinoma was unknown. An increase of PD-L1 expression was shown after chemotherapy in a retrospective study [9], which suggested the potential of treatment such as immune check point inhibitors after conventional chemotherapy as we treated four patients. Fortunately, our patients had no severe immune related adverse events (irAEs), however, we must pay closely attention to irAEs, especially given the autoimmune disorder with thymic carcinoma such as myasthenia gravis, they might be more likely to experience irAEs. The phase 2 study alerted the incidence of adverse events in thymic carcinomas were higher than in other tumors [4].

Here, we presented 4 patients with unresectable thymic carcinoma showing well response to nivolumab. Except for clinical trials, our case series were the first report of nivolumab for thymic carcinoma in real world clinical setting. Because the number of patients of published phase 2 study was small and this study was designed as a single arm study, the evidence of effect to thymic carcinoma has not been established. We must evaluate much more patients treated with immune therapy and need larger randomized trials.

Conflicts of interest statement

All authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2018.11.007.

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