

Therapeutic Potential of Docetaxel plus Cisplatin Chemotherapy for Myasthenia Gravis Patients with Metastatic Thymoma

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The prognosis of myasthenia gravis (MG) in association with invasive or metastatic thymoma is usually worse, and therapeutic options are quite limited. Here, we retrospectively reported the therapeutic effect of docetaxel plus cisplatin (docetaxel/cisplatin) chemotherapy in 7 MG patients with metastatic thymoma. Previously, all patients underwent thymectomy at the first onset of thymoma. After the metastasis of thymoma, none of the patients received thymectomy due to unresectable conditions after surgeon's evaluation for great risk of myasthenic crisis ($n = 5$) or patients' refusal ($n = 2$). All patients received docetaxel (75 mg/m^2) and cisplatin (70 mg/m^2) on day 1 (d1) every 21 days, with the cycle ranging from 1 to 4. After docetaxel/cisplatin chemotherapy, one patient achieved partial response, and 6 with stable disease of the tumors. The clinical symptoms of MG were alleviated in all patients, 2 with complete remission and the other 5 with marked improvement. Myelosuppression was the major adverse event, occurring in 2 patients (grade II and IV). MG relapse occurred in one patient during the follow-up. Our study presented a series of MG patients with metastatic thymoma who underwent docetaxel/cisplatin chemotherapy. Besides the improved/stabilized thymoma, markedly improvement of MG with the tolerable adverse events was achieved. Docetaxel/cisplatin chemotherapy appears to be an effective treatment for selected patients with MG in association with unresectable metastatic thymoma. Further follow-up of these patients and additional subjects will be needed to determine whether the therapeutic benefits are durable.

Keywords: chemotherapy; docetaxel plus cisplatin; myasthenia gravis; postoperative metastasis; thymoma
Tohoku J. Exp. Med., 2017 April, **241** (4), 281-286. © 2017 Tohoku University Medical Press

Introduction

Thymoma is a rare mediastinal neoplasm with an indolent growth pattern, yet local invasion and/or dissemination may occur. The estimated incidence of thymoma was 0.13/100,000 person years in the United States alone (Engels 2010). Although the aetiology of thymoma is still unknown, it has been suggested to be associated with autoimmune diseases, such as myasthenia gravis (MG) (Fujii 2013). About 30-50% of thymoma patients have been reported to develop MG, while the frequency of thymoma was 10-20% among the patients with MG (Romi 2011; Marx et al. 2015). Surgery has been well-established as the standard treatment for thymoma. Although the prognosis was more optimistic in MG without thymoma, both the clinical symptoms of MG and thymoma can be alleviated after thymectomy (Yu et al. 2012). However, postoperative recurrence or metastasis is still inevitable and not uncommon (Hishida et al. 2016), and few therapeutic options are available for effective treatment of relapsed or refractory

thymoma (Simonelli et al. 2015). Despite the recommendations for further resection, vast majority of patients will relapse again (Bott et al. 2011). In addition, a small but important proportion of patients are with unresectable metastatic thymoma. Thus, therapeutic options for these patients are with great clinical significance.

Thymic epithelial tumors are sensitive to chemotherapy (Lamarca et al. 2013). Systematic chemotherapy has been often employed in patients with relapsed or metastatic disease after local therapy such as surgery and radiation. Cisplatin is the most active single agent in thymic epithelial tumors. Cisplatin-based regimens have been reported to produce a 50%-100% response rate in naive patients (Venuta et al. 2003; Kim et al. 2004). Combination chemotherapy exhibited synergistic activity and caused a better response rate (Hernandez-Ilizaliturri et al. 2004; Giaccone 2005). Cisplatin-based combination regimens have been recommended for unresectable and relapsed thymoma. As a third-generation chemotherapy agent, docetaxel showed dramatic clinical activity against epithelial tumors (Gandara

Received December 21, 2016; revised and accepted March 14, 2017. Published online April 6, 2017; doi: 10.1620/tjem.241.281.

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et al. 2000; Oguri et al. 2004; Song et al. 2014; Watanabe et al. 2015). Combined chemotherapy with docetaxel and cisplatin (docetaxel/cisplatin) in a prospective Phase II trial led to a novel response in patients with advanced thymoma (Park et al. 2013). Here, we reported a serial of MG patients who underwent docetaxel plus cisplatin chemotherapy for metastatic thymoma with unresectable conditions or patients' refusal. In addition to the improved/stabilized thymoma, our results showed dramatic improvement of clinical symptoms of docetaxel plus cisplatin therapy in MG management.

Subjects and Treatment

This study retrospectively reviewed 7 patients suffering from MG and metastatic thymoma. All patients underwent docetaxel plus cisplatin chemotherapy at the Myasthenia Gravis Treatment Center of Hebei Province, First Hospital of Shijiazhuang (Hebei, China) during May 2013 to September 2015. This study was approved by the Ethical Committee of First Hospital of Shijiazhuang and written informed consents were obtained from all participants. MG was diagnosed on the basis of clinical symptoms and further supported by acetylcholine receptor antibody (AChR-Ab) test, neostigmine test, fatigue test, and electromyography tests (Li 2016). The severity of MG were evaluated according to Osserman classification (Osserman and Genkins 1971). Thymoma was diagnosed by chest computed tomography (CT) scan and further confirmed histopathologically. Pathological classification was based on the World Health Organization (WHO) histological classification of thymoma (Rosai and Sobin 1999). Clinical staging was performed according to Masaoka's staging system (Masaoka et al. 1981).

Previously, all patients underwent surgical resection after the first onset of thymoma, with 6 received open-heart surgery and 1 with minimal invasive thoracoscopic thymectomy. The histologic types of thymoma were B1 in 3 patients, and B2 and B3 in each 2 patients. Masaoka stage was I in 1 patient, II in 5, and III in 1 patient. 3 patients also received radiotherapy after thymectomy; no patients underwent chemotherapy. The relapse of thymoma occurred in all patients and diagnosed by CT scan. The median time from surgical resection after first-onset of thymoma to metastasis was 5.07 years, ranging from 0.84 to 29.59 years. In the meantime, patients were all suffered from relapsed MG. The median course of MG was 7.2 (1.5-30) years. Previous treatments of MG were as following: 6 patients were treated with pyridostigmine bromide, 2 with high-dose glucocorticoids. None patients received thymectomy due to unresectable conditions after surgeon's evaluations for great risk of myasthenic crisis) ($n = 5$) or patients' refusal ($n = 2$).

Docetaxel plus cisplatin was prescribed for treatment of metastatic thymoma in MG patients. Ridwelski et al. (2001) reported that a dosage higher than 80 mg/m² of docetaxel plus cisplatin was too toxic, and the combination

of docetaxel (75 mg/m²) and cisplatin (75 mg/m²) were used for locally advanced and metastatic gastric cancer. Similarly, in a prospective phase II trial of docetaxel/cisplatin in the induction chemotherapy on thymic epithelial tumors, the treatment regimen consisted of docetaxel 75 mg/m² and cisplatin 75 mg/m² (Park et al. 2013). Roka and his colleges (2004) reported a 31-year-old man with extra-thyroidal tumor who relapsed several times and finally metastasized to the lung was completely treated with the combination of docetaxel (75 mg/m²) and cisplatin (60 mg/m²) chemotherapy. Therefore, our center used the dosage of docetaxel (75 mg/m², d1) and cisplatin (70 mg/m², d1) every 21 days.

Tumor response is defined as complete remission (CR), partial remission (PR), stable disease (SD) and disease progression (PD) according to the WHO criteria (World Health Organization 1979). Clinical outcome of MG was assessed using the clinical absolute and relative scoring system according to our previous report (Liu et al. 2014). Briefly, this scoring system is based on the combination of clinical absolute scoring system and clinical relative scoring system. The clinical absolute scoring system is used to evaluate the clinical severity of MG considering the frequently involved muscles including muscles of eye up-gazing, horizontal movement of eye-balls, upper and lower limbs, facial expression, chewing and swallowing, and respiratory function (Liu et al. 2014). The clinical relative scoring (CRS) system is applied to evaluate the therapeutic effectiveness. It is calculated as following: the clinical relative score (CRS) = (pretreatment absolute score - post-treatment absolute score)/pretreatment absolute score. The treatment effect is divided into five categories: complete remission (CR, CRS $\geq 95\%$), basic remission (BR, $80\% \leq \text{CRS} < 95\%$), marked improvement (MI, $50\% \leq \text{CRS} < 80\%$), improvement (IM, $25\% \leq \text{CRS} < 50\%$), and ineffectiveness (IE, CRS $< 25\%$) (Liu et al. 2014). The adverse events were recorded and assessed during the treatment according to the WHO criteria.

Results

Seven patients (male, 3 patients) with metastatic thymoma-associated MG were treated by docetaxel plus cisplatin chemotherapy. The clinical characteristic of the patients are summarized in Table 1. The median age of the patients underwent docetaxel/cisplatin chemotherapy was 49 years, ranging from 28 to 58 years. All patients had metastatic thymoma as determined by CT scan or biopsy. Three patients were diagnosed with mediastinal metastases and the other 4 patients were with pleural metastases. Before the treatment, 5 patients were at stage IV (late severe MG), and the remaining 2 patients were stage IIB (moderate generalized or faciopharyngeal form) according to the Osserman classification.

Docetaxel plus cisplatin was prescribed for metastatic thymoma, and the cycle of chemotherapy ranged from 1 to 4 (Table 2). One patient was further treated by radiotherapy

Table 1. Baseline data of MG patients with metastatic thymoma.

Patient #	Age (years)	Sex	MG course (years)	Osserman classification	Metastasis	ECOG performance
1	28	Female	4.17	IV	Pleura	3
2	58	Male	30	IV	Pleura	2
3	40	Female	2	IIB	Mediastinum	1
4	51	Male	7.17	IV	Mediastinum	3
5	51	Male	9	IV	Mediastinum	3
6	37	Female	8	IV	Pleura	1
7	49	Female	1.5	IIB	Pleura	1

MG, Myasthenia gravis.

Table 2. Outcome of MG patients with metastatic thymoma.

Patient [#]	Docetaxol plus cisplatin (cycle)	Other treatments	Time to chemotherapy (months) ^a	Thymoma response	AChR-Ab				CRS	MG response	Adverse reaction	Follow up (months)
					Before	After	Before	After				
1	3	No	7.90	SD	15.09	13.34	21	6	MI	Grade IV myelosuppression	16.1	
2	2	No	12.77	SD	11.81	10.37	19	4	MI	No	18.3	
3	1	No	21.40	SD	8.13	2.2	7	0	CR	No	21.2	
4	2	RT + IA	0.23	SD	6.62	5.95	18	4	MI	Grade II myelosuppression	8.9	
5	4	No	2.03	SD	1.89	8.61	23	11	MI	No	32.7	
6	2	No	0.03	PR	9.05	3.82	16	4	MI	No	13.2	
7	1	No	1.57	SD	3.83	1.1	8	0	CR	No	36.3	

RT, Radiotherapy; IA, Immunosuppressive agent; SD, Stable disease; PR, Partial remission; AChR-Ab, Antiacetylcholine receptor antibodies; MG, Myasthenia gravis; MI, Marked improvement; CR, Complete remission.

^aTime from thymoma metastasis to docetaxol plus cisplatin chemotherapy.

[#]Patient number.

and immunosuppressant (#4). A median time from tumor metastasis to chemotherapy was 2 months, ranging from 0 to 22 months. After chemotherapy, one patient with metastatic thymoma achieved partial response and the remaining 6 had stable disease. Patients with smaller metastatic lesions were monitored by CT scanning during the follow-up. Ones who had large lesions were further treated by steroid pulse therapy, radiotherapy, or interstitial brachytherapy.

With respect to the MG, the clinical symptoms were remitted in all the 7 patients. Two patients achieved complete remission and the other 5 patients with marked improvement. Serum AChR-Ab levels were decreased in all except one patient (#5), who experienced MG relapse 2 months after treatment and gave up further treatment. The median duration of follow-up was 18.3 months (range: 8.9-36.3). Myelosuppression was the major adverse event, occurring in 2 patients, one with grade II and the other with grade IV. Recombinant human granulocyte colony stimu-

lating factor was prescribed for grade II myelosuppression. The first class nursing care was provided to the patient with the grade IV myelosuppression. All patients were stabilized and no deaths occurred during the follow-up.

Discussion

Systematic chemotherapy with docetaxel/cisplatin is proved to be safe and effective in various types of cancer, including advanced non-small cell lung cancer, recurrent endometrial cancer, and thymic epithelial tumors (Shintani et al. 2001; Ohe et al. 2004; Li et al. 2006; Huang et al. 2009; Ninomiya et al. 2016). Besides, a 31-year-old man with repeatedly recurrent extrathyroidal tumor and finally metastasized to the lung was completely treated by docetaxel (75 mg/m²) and cisplatin (60 mg/m²) chemotherapy (Roka et al. 2004). In patients with thymic carcinoma, one of the most common regimens used was indicated to be cisplatin plus docetaxel (Huang et al. 2009). Therefore, docetaxel plus cisplatin was prescribed in our study for

treatment of thymoma-associated MG with postoperative metastasis.

All patients had partial response (1 patient) or stable diseases (6 patients) of thymoma after combination chemotherapy. The objective response rate (ORR) was relative low in these patients. The low ORR may be caused by the complexity of patients' status with metastasis of thymoma and the combination of MG. As a consequence of the rarity of thymoma, especially considering the metastatic thymoma, relative knowledge of therapies is mainly reported by case reports. Therefore, there has been less report of ORR of cisplatin plus docetaxel for patients with metastatic thymoma without MG till now. However, our results was partially consistent with a previous prospective phase II clinical trial carried out in patients with advanced thymic epithelial tumors (Masaoka Stage III/IV) (Park et al. 2013). The results showed that all patients achieved partial response or stable disease. In a subset of patients with thymic carcinoma, 12 patients (67%) achieved partial response and the other 6 achieved stable disease. Meanwhile, 5 patients with thymoma (55.6%) had partial response and the remaining 4 had stable disease (Park et al. 2013). A previous study of a 57-year-old man with Masaoka stage III thymic carcinoma showed the stable disease achieved after cisplatin plus docetaxel and irradiation therapy (Momozone et al. 2016). However, a minor response was observed in a 40-year-old man with thymic squamous cell carcinoma when cisplatin and docetaxel combination therapy was administered (Makimoto et al. 2014). The conflicting results can be partially explained by tumor types, stage and status of the thymoma, and the accompanied autoimmune diseases. Still, our study did show potential benefit effect of docetaxel plus cisplatin chemotherapy on management of metastatic thymoma.

Interestingly, the symptom of MG was also found to be markedly improved by docetaxel plus cisplatin therapy, with the decreased AchR-Ab levels and clinical relative scores. The increased AchR-Ab titer may associate with the less remission or exacerbation of the MG (Hayashi et al. 1995). One patient developed MG relapse during the follow-up, in which the serum AchR-Ab level was positive before treatment and elevated after docetaxel plus cisplatin chemotherapy. The results above suggested the potential role of AchR-Ab monitor in proper management and prognostic prediction of MG patients. To our knowledge, the beneficial effect of docetaxel plus cisplatin chemotherapy on clinical management of MG was less reported. The potential mechanism is complex, and may be associate with the immunosuppressive effect of docetaxel (De Santis et al. 2000; Bear et al. 2003; Brain et al. 2005). In addition, more studies are needed to further clarify the efficiency and molecular mechanisms of docetaxel plus cisplatin chemotherapy in patients with MG.

Chemotherapy has long been associated with treatment-related toxicity. The adverse events observed may vary with the studies. Myelosuppression was considered to be

the major toxicity associated with docetaxel therapy (Albany and Sonpavde 2015). Nausea, myelosuppression, fatigue, and alopecia were the most common adverse events in non-small-cell lung cancer patients receiving cisplatin plus docetaxel (Mitsudomi et al. 2010). A multicenter phase II trial of docetaxel plus cisplatin neoadjuvant chemotherapy indicated that nausea, alopecia, leukocytopenia, and granulocytopenia were the most frequent side effects in stage IIIA pN2 non-small-cell lung cancer patients (Betticher et al. 2003). During the combination of docetaxel and cisplatin therapy, leukopenia was observed as the most frequent haematological toxicity in patients with locally advanced and metastatic gastric cancer (Ridwelski et al. 2001). In patients with advanced thymic epithelial tumors (Masaoka Stage III/IV), docetaxel plus cisplatin chemotherapy caused the major adverse events of grades III/IV neutropenia (8, 29.6%), diarrhea (3, 11.1%), grade III leukopenia (2, 7.4%), and nausea (2, 7.4%) (Park et al. 2013). In the present study, myelosuppression was the major adverse event and occurred in 2 patients (grade II and IV), and the symptoms were well tolerated by the patients. Our results infer the therapeutic potential of docetaxel plus cisplatin chemotherapy for treatment of MG patients with metastatic thymoma.

In conclusion, our study presented a case series of MG patients with metastatic thymoma who underwent combination chemotherapy with docetaxel/cisplatin. In addition to the improved/stabilized thymoma, the combined chemotherapy markedly improved clinical symptoms of MG. Myelosuppression was the major adverse event observed and was well tolerated. Docetaxel/cisplatin chemotherapy appears to be an effective treatment for selected patients with MG in association with unresectable metastatic thymoma. Further follow-up of these patients and additional subjects will be needed to determine whether the therapeutic benefits are durable.

Acknowledgments

Guoyan Qi and Peng Liu contributed equally to this work and should be recognized as co-first authors. This work was supported by Shijiazhuang Science and Technology Bureau Foundation (Grant no.131460613), Science and Technology Agency Foundation of Hebei Province (Grant no.14277758D), Natural Science Foundation of Hebei Province (Grant no. H2015106020), and Key Project of Hebei Provincial Administration of Traditional Chinese Medicine (Grant no.2014221).

Conflict of Interest

The authors declare no conflict of interest.

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