

Research Article

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Docetaxel/cisplatin therapy in myasthenia gravis with hypertension/diabetes

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Abstract: Background: Therapeutic options for thymoma-associated myasthenia gravis (MG) patients complicated with hypertension and/or diabetes post thymectomy are often conventional steroids. As the prevalence of diabetes and hypertension globally increases, other therapeutic options for these patients are of great importance. Material/methods: 9 patients with thymoma-associated MG complicated with hypertension and/or diabetes after thymectomy were administered 75 mg/m² of docetaxel and 70 mg/m² of cisplatin on day 1. The treatment could be repeated at 3-week intervals, ranging from 1 to 4 cycles according to the status of the patients. Therapeutic efficacy and side effects were evaluated. Results: 2 patients were complicated with type 2 diabetes, 6 with hypertension, and 1 with both diabetes and hypertension. After docetaxel/cisplatin therapy, the MG symptoms were markedly improved in all patients (2, complete remission; 3, basic remission; 3, marked improvement; 1, improvement). Acetylcholine receptor (AChR) antibody levels were decreased in 8 patients. Minor adverse effects were observed in 2 patients, 1 with Grade II gastrointestinal reaction, and the other with pulmonary infection. Conclusion: Docetaxel plus cisplatin might be an effective therapeutic option for thymoma-associated MG patients complicated with hypertension /diabetes post thymectomy without worsening thymoma and hypertension / diabetes.

Keywords: Myasthenia gravis; Treatment; Thymectomy; Hypertension; Diabetes

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1 Introduction

Myasthenia gravis is an autoimmune disorder induced by neurotransmission defects at the neuromuscular junction, which is characterized by muscle weakness and fatigue. It has been well-documented that approximately 10-15% of MG patients also suffer from thymoma, and nearly all these patients have detectable AChR antibodies and generalized disease [1]. Approximately 30% of patients with thymoma develop MG, and even more have AChR antibodies without MG [2]. Thymectomy has been recommended for MG patients with thymoma, which could not only reduce the risk of proliferation and invasion, but also improve MG symptoms for most patients [3]. For patients either not responding to thymectomy or suffering from MG recurrence post thymectomy, corticosteroids are the most commonly used and most effective immunosuppressive treatments.

Corticosteroids are the first line treatment of mild to moderate MG, and have been considered to be the standard therapy currently. Though MG patients could do well and have well-controlled disease with corticosteroid, either alone or combined with other immunosuppressive agents [4], most need long-term and even life-long treatment with low-dose steroids treatment. Long-term steroids use will increase the appetite of patients, which increases the risks of central obesity, glucose intolerance and hypertension [1, 3].

As the prevalence of hypertension and diabetes globally increases [5, 6], the number of thymoma-associated MG patients accompanied by hypertension and/or diabetes is inevitably growing. The presence of hypertension/diabetes poses an additional burden to a patient with myasthenia gravis. Though hypertension and/or diabetes is not absolute contraindication to steroids, long-term use of steroids would definitely increase the difficulty on the control of blood pressure and/or glucose as hyperglycemia and hypertension are the major side effects of long-term steroids use. This would lead to additional medication in order to control blood pressure/glucose, which increases the treatment cost for patients. Moreover, it also potentially increases the risk of cardiovascular

diseases-related death [5], considering that diabetes and hypertension are major predisposing factors. Thus, other therapeutic options for this group of patients are of great clinical importance.

Based on the clinical experiences at our center since 2005, we have observed favorable responses of MG after docetaxel/cisplatin therapy for thymoma-associated MG patients. Even in MG patients with unresectable metastatic thymoma, the MG symptoms could be significantly improved after docetaxel plus cisplatin therapy [7]. In the present study, we report the therapeutic effects and adverse events of docetaxel plus cisplatin therapy in a serial of thymoma-associated MG patients complicated with hypertension and/or diabetes who did not respond to thymectomy or suffered from MG recurrence post thymectomy.

2 Subjects and methods

During the period between January 2014 and June 2015, 9 patients with thymoma-associated MG complicated with hypertension and/or diabetes, either not responding to thymectomy or suffering from MG recurrence, underwent docetaxel plus cisplatin treatment at the Myasthenia Gravis Treatment Center of Hebei Province, First Hospital of Shijiazhuang (Hebei, China). The study was approved by the Ethical Committee of the First Hospital of Shijiazhuang, and informed consent was obtained from all the 9 patients.

Thymoma was diagnosed *via* computed tomography (CT) scan, and histological confirmation was done based on the World Health Organization (WHO) histological classification of thymoma [8]. The clinical and pathologic staging of thymoma was done according to the Masaoka's staging system [9]. The diagnose of MG was based on the clinical symptoms and other examinations including methyl sulfate neostigmine test, electromyography, and serum antibody tests [10]. The severity and classification of MG were assessed in accordance with modified Osserman scale [11]. Prior to the docetaxel and cisplatin treatment, all patients received surgical resection of thymoma (7 with thoracotomy; 2 with minimally invasive thoracoscopic thymectomy). MG symptoms were not alleviated in 4 patients, and MG recurrence occurred in the other 5 patients. The longest MG course was 96 months, with the median of 18 months. The relative information of medication on blood pressure and/or glucose control in all patients has been provided in Table 1.

All patients were treated with 75 mg/m² of docetaxel and 70 mg/m² of cisplatin on day 1, and the treatment could be repeated at 3-week intervals [7, 12-14]. The treatment ranged from 1 to 4 cycles, according to the status of the patients. Therapeutic effects of docetaxel/cisplatin on MG symptoms were evaluated based on the clinical relative scoring (CRS) system in China as described previously [15, 16]. Adverse effects during the treatment were evaluated in accordance with the World Health Organization criteria.

3 Results

Among the 9 thymoma-associated MG patients, 2 were complicated with type 2 diabetes, 6 with hypertension, and 1 with both diabetes and hypertension. The median age was 59 years, ranging from 41 to 77 years. The characteristics of each patient were shown in Table 1. Previously, all patients underwent surgical resection of thymoma (7 with thoracotomy; 2 with minimally invasive thoracoscopic thymectomy). MG symptoms did not alleviate in 4 patients, and the other 5 suffered from MG recurrence. The median course of MG was 18 months, ranging from 9 to 96 months. Before the docetaxel/cisplatin therapy, 8 patients were stage IIB, and the remaining 1 patient was stage I according to the Osserman classification. The median time from thymectomy to docetaxel/cisplatin therapy was 4 months, ranging from one to 55 months.

The cycle of docetaxel/cisplatin treatment ranged from 1 to 4 (median, 2 cycles), as shown in Table 2. One patient also received radiotherapy (#3), and 1 patient underwent 2 courses of plasmapheresis (#4). After docetaxel/cisplatin therapy, the clinical symptoms of MG were significantly improved in all patients, including 2 patients with complete remission (CRS \geq 95%), 3 with basic remission (80% \leq CRS < 95%), 3 with marked improvement (50% \leq CRS < 80%), and 1 with improvement (25% \leq CRS < 50%). The levels of serum AChR antibodies (AChR-Ab) were reduced in 8 patients; while slight increase was observed in 1 patient (#2) (Table 3). The patients were followed up to 29 months, with a median duration of 18 months. MG recurrence occurred in patient #3 one year after docetaxel/cisplatin therapy. No influence of chemotherapy on blood pressure/glucose has been observed, and all patients maintained previous treatment protocols on blood pressure/glucose control. Minor adverse effects were observed in only 2 patients, including 1 patient with Grade II gastrointestinal reaction (#2), and the other with pulmonary infection (#3).

Table 1: Characteristics of patients before docetaxel/cisplatin treatment.

Patient #	#1	#2	#3	#4	#5	#6	#7	#8	#9
Age/Sex	63 F	57 F	41 M	66 M	52 M	77 M	72 F	59 M	50 M
Duration of MG (months prior)	12 mos	18 mos	72 mos	96 mos	24 mos	60 mos	10 mos	3 mos	5 mos
MG severity (Before treatment)	II B	II B	II B	II B	II B	II B	II B	I	II B
Thymoma									
Masaoka stage	II	III	I	I	II	II	I	I	II
WHO type	B3	B2/B3	B1	B3	B3	B2	B2	B2	B2
Thymectomy (months prior)	18 mos	1 mo	50 mos	1 mo	7 mos	55 mos	4 mos	1 mo	1 mo
Diabetes	\	\	Type 2	\	\	Type 2	Type 2	\	\
Medication for DM	\	\	insulin	\	\	Acarbose glibenclamide	insulin	\	\
Hypertension	Stage 3	Stage 2	\	Stage 3	Stage 3	\	Stage 3	Stage 3	Stage 2
Medication for Hypertension	Metoprolol	Kato Pury Nifedipine	\	Nifedipine	Irbesartan Felodipine Metoprolol	\	Nifedipine Betaloc	Adalat Valsartan	Metoprolol Enalapril Nitrendipines
Additional features before treatment		Chronic hepatitis C; pressure ulcers; right lower limb amputation		Parkinson's disease				Gout	
AchR antibody before treatment	7.62	6.92	13.99	8.69	8.53	11.19	13.43	9.97	7.38

Severity of MG is rated according to modified Osserman classification.
MG, myasthenia gravis; WHO: World Health Organization.

4 Discussion

In the present study, we revealed that 9 thymoma-associated MG patients complicated with hypertension and/or diabetes had favorable responses to docetaxel plus cisplatin therapy. Previously, these patients did not respond to thymectomy or suffered from MG recurrence post thymectomy. The median number of docetaxel/cisplatin treatment cycle was only 2, ranging from 1 to 4. After treatment, 8 out of the 9 (88.9%) patients were achieved at least marked improvement, with 2 patients achieved complete remission. Minor adverse effects were observed in only 2 patients, including 1 patient with Grade II gastrointestinal reaction, and the other with pulmonary infection.

Conventional immunosuppressive treatment has been the first-line therapy for adult MG patients, and long-term and even life-long treatment with low-dose steroids is required for most patients. It has been reported that MG patients with corticosteroids treatment had a 1.46-fold

increased risk of developing diabetes mellitus as compared with non-MG cohort; while those without corticosteroids had no increase risk of DM [17]. In our study, we found that docetaxel/cisplatin treatment did not influence the medication for hypertension/DM.

Systematic chemotherapy with docetaxel and cisplatin has been used as one of the most common regimens in patients with thymic carcinoma [18]. We have used this regimen in patients with thymic carcinoma back to 2005. Interestingly, we have found that the responses of thymic carcinoma were minor to moderate, but the symptoms of MG were markedly improved by this regimen. Even in MG patients with unresectable metastatic thymoma, the symptom of MG could be markedly improved after docetaxel/cisplatin therapy [7]. Thus far, docetaxel/cisplatin therapy has proved to be generally safe and well tolerated in MG patients with thymoma, based on the observations at our center since 2005. Of the 9 patients treated at our center, almost half of patients (n=4, 44.4%) only

Table 2: Outcome of patients after docetaxel plus cisplatin therapy.

Patient #	#1	#2	#3	#4	#5	#6	#7	#8	#9
Docetaxel/cisplatin (cycle)	1	2	2	2	4	3	1	2	3
Other treatments			RT	PP					
CRS									
Before	10	26	15	4	21	10	10	9	19
After	0	8	2	0	4	5	6	2	2
Blood pressure*									
Before	118/87	135/75	139/92	120/80	154/97	130/60	136/78	143/88	132/101
After	\	97/62	134/70	120/80	126/83	130/60	137/70	138/90	127/71
Blood glucose#									
Before	4.3	6.4	18.3	7.2	4	5	7.8	5.4	5.8
After	\	6.1	13.6	6.2	4	7.2	6.4	5.4	3.4
MG response	CR	MI	BR	CR	BR	MI	IM	MI	BR
Adverse effects		Grade II gastrointes- tinal reaction	Pulmonary infection						
Follow up (Months)	28	11	14	22	29	23	15	14	18

* Blood pressure in patients with hypertension is detected under daily antihypertensive medication; # Blood glucose in patients with diabetes is detected with relative medication for DM.

RT, radiotherapy; PP, plasmapheresis; CRS, clinical relative score; MG, myasthenia gravis; AchR-Ab, Antiacetylcholine receptor antibodies; CR, Complete remission; BR, basic remission; MI, Marked improvement; IM, improvement.

Table 3: Change in AchR-Ab levels.

Patient #	Pre-docetaxel/cisplatin	Post docetaxel/cisplatin
#1	7.62	0.55
#2	6.92	7.66
#3	13.99	10.5
#4	8.69	4.54
#5	8.53	7.28
#6	11.19	10.57
#7	13.43	2.72
#8	9.97	1.8
#9	7.38	7.29

AchR-Ab, Antiacetylcholine receptor antibodies.

received 2 cycles of docetaxel/cisplatin treatment. Over the long run, docetaxel/cisplatin treatment may avoid certain stress in control of bodyweight, blood pressure and blood glucose of long-term treatment with low-dose immunosuppression, with relative short period of treatment. This would especially benefit MG patients complicated with diabetes and/or hypertension.

All these patients have returned to full active lives without immunosuppressive medications. 88.9% (n=8) patients have achieved at least marked improvement, with 2 patients achieved complete remission. Till now, the longest follow-up so far is 2.4 years, and only 1 patient suffered from MG recurrence. All the 9 patients had antibodies to AChR. The AchR-Ab levels were decreased, but AchR antibody responses still existed in all patients after docetaxel/cisplatin therapy. Our results indicate that docetaxel/cisplatin therapy could produce marked clinical improvement without complete elimination of the AchR-Ab response. Similar observations have been reported by Daniel et al. They reported that clinical improvement was achieved in patients with refractory myasthenia treated with high-dose cyclophosphamide, without complete elimination of AchR antibody response [19, 20].

Nevertheless, docetaxel/cisplatin treatment may have certain adverse effects. Though the adverse effects observed varied with studies, myelosuppression and gastrointestinal reaction were considered to be the major toxicity associated with chemotherapy [21-23]. Myelosuppression, nausea, fatigue, and alopecia have been reported

to be the most common adverse effects in patients with non-small-cell lung carcinoma treated with cisplatin plus docetaxel [24]. Park et al. reported that grades III/IV neutropenia, grade III leucopenia, diarrhea and nausea were the major side effects in patients with advanced thymic epithelial tumors treated with docetaxel plus cisplatin chemotherapy. Of the 9 patients treated with docetaxel/cisplatin in this report, 1 patient developed Grade II gastrointestinal reaction, and one had pulmonary infection. No obvious side effects were observed in the other 7 patients. Our results infer that docetaxel/cisplatin therapy is generally safe and well tolerated in thymoma-associated MG patients complicated with diabetes and/or hypertension.

To sum up, in thymoma-associated MG patients complicated with hypertension and/or diabetes, who also either did not respond to thymectomy or suffer from MG recurrence postoperatively, docetaxel/cisplatin therapy may produce impressive and potentially long-term benefits with tolerable side effects. Over the long run, docetaxel/cisplatin treatment may avoid additional stress in the control of bodyweight, blood pressure and blood glucose causing by long-term low-dose immunosuppressive treatment. However, the sample size of this study is relative small, which may affect the generalization of our results. Further additional subjects with longer follow up are needed to test the durability of therapeutic benefits with this regimen.

Conflict of interest: The authors declare no conflict of interest.

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