Pretreatment with different doses of dexamethasone in the prevention of docetaxel-induced hypersensitivity

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Abstract: This study aimed to evaluate the efficacy and safety of dexamethasone pretreatment regimen with different doses in the prevention of docetaxel-induced hypersensitivity reaction (HSR). One hundred and sixty-two patients who had malignant tumors as determined by histology and/or cytology and received docetaxel treatments at least 2 cycles, were randomized into two groups. There were 90 patients in the study group and 72 patients in the control group. In the study group, patients received 4.5mg of oral dexamethasone once a day. Patients in the control group received 8 mg of dexamethasone twice a day. All patients received dexamethasone for 3 days, from the day before docetaxel treatment to the day after docetaxel treatment. The endpoints were hypersensitivity reaction (HSR) and other adverse effects, which were determined according to common terminology criteria for adverse event v3.0 (CTCAE 3.0). In the study group, 10 patients had HSRs (11.1%). While in the control group, 7 patients had HSRs (9.7%), and the main clinical symptoms of HSR were rash (3.1%), fever/chill (2.5%), angioedema (1.9%), chest discomfort (1.9%) and hypotension (0.6%). There was no statistically significant difference between these two groups (P=0.774). There was no significant difference in the incidence rate of adverse effect between patients in the study group and in the control group. Those adverse effects included neutropenia, decreased hemoglobin, nausea, vomiting, fatigue and fluid retention. Since no significant difference in the HSR incidence between these two groups has been found, 4.5mg of dexamethasone (qd) is as efficient and safe as 8mg (bid).

Keywords: Dexamethasone, docetaxel, hypersensitivity reaction, premedication regimen.

INTRODUCTION

Docetaxel is a widely used chemotherapy drug in clinics for the treatment of various types of cancer (Lehoczky *et al*., 2005; Cortes and Roché, 2012; Colloca *et al*., 2012; Zhao and Astruc, 2012). However, hypersensitivity reaction (HSR) is an unmet challenge of docetaxel treatment (Kadoyama *et al*., 2011). There is no effective approach to prevent docetaxel induced HSRs (Kitada *et al*., 2012). The current premedication strategy for reducing the incidence and severity of HSR is the oral administration of 8 mg of dexamethasone twice a day for 3 days (before, during and after the day of docetaxel treatment) (TIC, 2006). With the increase of weekly docetaxel treatment, prolonged administration of high dose dexamethasone will lead to immunosuppression, infection and other adverse effects (Martín *et al*., 2013; Poi *et al*., 2013). This study was to determine whether docetaxel induced side effects could be prevented with a reduced dose of dexamethasone premedication.

METHODS

Patient inclusion criteria

Patients had malignant tumors as determined by histology and/or cytology, and received docetaxel treatments. The patients were between 18 and 77 years old and had a Karnofsky performance status (KPS) score ≥60. Those patients were expected to survive longer than 3 months, and had normal liver function (AST or ALT within 1.5 times the upper limits of normal), blood count, renal function and electrocardiogram. This study was conducted in accordance with the declaration of Helsinki and approved from the Ethics Committee of Anhui Medical University. Written informed consent was obtained from all participants.

Patient exclusion criteria

Patients with one of those conditions were excluded from the study: pregnant or nursing, active tuberculosis or other infections, history of mental disorder, recent hormone treatment, unstable diabetes, or corticosteroid contraindications.

Treatment strategy

All patients treated with doxtaxel were divided into two groups. Patients in the study group received 4.5mg of dexamethasone once a day while those in the control group received 8mg of dexamethasone twice a day. Dexamethasone was administered orally on the day before, during and after docetaxel treatment. Each patient received at least two cycles of docetaxel treatment.

Criteria of adverse effects

Hypersensitivity reaction and other adverse effects were determined according to common terminology criteria for adverse event v3.0 (CTCAE 3.0) (National Cancer Institute, 2006).

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STATISTICAL ANALYSIS

All data were analyzed by SPSS 11.5 software. The difference between two groups was determined by χ^2 and Fisher's exact test. A statistically significant difference was set as $P<0.05$.

RESULTS

Patients

The enrolled patients were from those who were hospitalized and received docetaxel treatment at the Department of Oncology, Second Hospital of Anhui Medical University between October 2009 and December 2011. Among those patients, 166 of them met the enrollment criteria. Four patients did not finish minimal 2 cycles of treatment. There were 162 patients in this study with a total of 478 docetaxel treatment cycles. Ninety-four of them were male and 68 of them were female with age range from 18 to 75. The mediam age of those patients was 56.

Incidence of hypersensitivity reaction

Overall, 17 out of 162 (10.5%) docetaxel treated patients had hypersensitivity reactions (HSRs). The study group had 90 patients and 10 of them had HSRs (11.1%). Seven out of 72 (9.7%) patients in the control group had HSRs. No statistically significant difference in the incidence rate of HSR was found between those two groups (table 1)

Clinical symptoms of HSR

The main clinical symptoms of HSR were rash (3.1%), fever/chill (2.5%), angioedema (1.9%), chest discomfort (1.9%) and hypotension (0.6%) (table 2).

Docetaxel treatment strategy and incidence of HSR

Patients received one of two docetaxel treatment strategies, weekly (25mg/m^2) and triweekly (75mg/m^2). The HSR incidence rates in the patients receiving weekly and triweekly treatments were 11.5% and 9.6% respectively in the study group. The HSR incidence rates in the patients receiving weekly and triweekly treatments were 11.4% and 8.1% respectively in the control group. No statistically significant difference between the study group and control group was found (table 3).

Patient's age and incidence rate of HSR

Thirty patients in the study group were 65 or older. Among them, 3 (10.0%) had HSRs. Sixty patients in the study group were younger than 65 and 7 (11.7%) of them had HSRs. In the control group, 26 patients were 65 or older, and 2 (7.7%) of them had HSRs. Forty-six patients in the control group were younger than 65 and 5 (10.5%) of them had HSRs. Again, no statistical difference in age distribution of patients with HSRs between the study group and control group was found (table 3).

Adverse effects

There was no significant difference in the incidence rate of adverse effect between patients in the study group and in the control group. Those adverse effects included neutropenia, decreased hemoglobin, nausea, vomiting, fatigue and fluid retention. However, the incidence rates of muscle pain and insomnia/excitement in patients receiving weekly docetaxel treatment were significantly higher in the control group than those in the study group. The incidence rates of these adverse effects did not differ in the control group and study group with triweekly docetaxel treatments (table 4).

DISCUSSION

The incidence rate of allergic or hypersensitivity reactions to docetaxel is 1-10% with about 3% severe reactions. The main symptoms of hypersensitivity are rash, chest discomfort/breathing difficulty and low blood pressure (Belani, 2001; Nabholtz *et al*., 2003). The underlying mechanism of these hypersensitivity reactions is not clear. Although the symptoms are similar to those of type I hypersensitivity, most patients do not have sensitization stage during the first time of docetaxel treatment, suggesting that these hypersensitivity reactions are not IgE-mediated. It is likely that the hypersensitivity is caused by the direct effect of the drug on immune cells (Lenz, 2007). However, the clinical manifestation of docetaxel caused HSRs overlaps with the infusion reaction, which makes it difficult to distinguish these two types of reaction. Therefore, the treatment strategy for the prevention of docetaxel caused HSRs has been controversial. There is no consensus on the dosage of dexamethasone in the prevention of docetaxel caused HSRs (Baker *et al*., 2008). Recent reports in the literatures indicate that prolonged premedication of dexamethasone in patients receiving taxane treatments can cause severe lymphopenia, dermatitis and thrombophlebitis, induce or exacerbate infections and increase the risk of pulmonary cryptosporidiosis (Verweij *et al*., 1994; Zanotti *et al*., 2001). Therefore, further studies on the optimal dose of dexamethasone in the prevention of docetaxel caused HSRs are needed. This study was meant to serve this purpose.

During recent years, some researchers have conducted studies in this aspect. However, studies with a large case number were only conducted in paclitaxel treated patients. Quock *et al*. (2002) reported a case study with 358 patients receiving paclitaxel treatment (a total of 1608 cycles). Those patients were given 10mg of dexamethasone by intravenous injection during the first treatment cycle. If no HSR occurred, the patients would not receive any premedication of dexamethasone in the subsequent treatments. Paclitaxel treatment was stopped if the patient had HSR. In that study, 344 patients finished all cycles of treatment without HSR and the incidence rate

Table 1: Distribution of 17 patients with HSRs

	Cases	NCI-CTC3.0		%	p
		I~II	III~IV		
HSR during 1st treatment cycle	15	14	1	88.2	
HSR during or after 2nd treatment cycle	2	2	0	11.8	<0.001
Age					
<65 (n=106)	12	11	1	11.3	
≥65 (n=56)	5	5	0	8.9	0.637
History of paclitaxel treatment					
Yes (n=12)	1	1	0	8.3	
No (n=150)	16	15	1	10.7	1.000 [a]
Dexamethasone dose					
4.5 mg (n=90)	10	14	1	11.1	
8 mg (n=72)	7	12	0	9.7	0.774
Docetaxel dose					
25 mg/m^2 (n=104)	12	12	0	11.5	
75 mg/m^2 (n=58)	5	4	1	8.6	0.561

Table 2: Symptoms of HSR in two groups

Symptom	N	%	Study group (n=90)		Control group (n=72)		χ^2	p
			n	%	n	%		
Rash (with or without itching)	5 [a]	3.1	3	3.3	2	2.9		1.000 [b]
Angioedema	3	1.9	2	2.2	1	1.4		1.000[b]
Fever/Chill	4	2.5		3.3	2	2.9		1.000[b]
eChest discomfort	3	1.9	1	1.1	2	2.9		0.845[b]
Hypotension	2	0.6	1	1.1	0	0		
Total	17	10.5	10	11.1	7	9.7	0.082	0.774

Table 3: Docetaxel treatment strategy and incidence rate of HSR

	Study group		Control group		*p*
	n	%	n	%	
Docetaxel treatment strategy					
Weekly	8 (8/69)	11.6	4 (4/35)	11.4	1.000 [a]
Triweekly	2 (2/21)	9.5	3 (3/37)	8.1	1.000 [a]
Age					
≥65	3 (3/30)	10.0	2 (2/26)	7.7	1.000 [a]
< 65	7 (7/60)	11.7	5 (5/46)	10.9	0.898 [a]

Fisher's exact test

of HSR was 3.9% (14/358). No study in the docetaxel treated patients with a similar sample number has been reported. Tsavaris *et al*. (2008) have reported that in 60 docetaxel treated patients, premedication with 4 mg of an antihistamine drug, dimethindene maleate, by intravenous injection led to the successful completion of the treatment without HSR. Joshua *et al*. (2005) reported in a study with 20 docetaxel treated patients that intravenous injection of 4-8 mg of dexamethasone 30 min before the treatment could effectively prevent HSR.

In this study, we investigated the effect of premedication with a reduced dose of dexamethasone. Patients in the study group received 4.5mg of dexamethasone while patients in the control group received regular 8 mg of dexamethasone. Patients in neither group received H1 or H2 blockers. The study group had 90 patients who met the enrollment criteria. The incidence rate of HSR was 11.1% in this group of patients. The control group had 72 patients and 9.7% of them developed HSRs. The difference in the incidence rate of HSR was not statistically significant between these two groups. This result is consistent with what has been reported in China and other countries. We further investigated whether there was a difference in the HSR incidence between two groups of patients in respect to the docetaxel dosage. Regardless of the treatment dosage of docetaxel, no difference in the HSR incidence between the control group and study group was found. This result indicates that the incidence rate of HSR does not differ whether the

Table 4: Comparison of adverse side effects in patients receiving weekly or triweekly docetaxel treatments between the control group and study group

Adverse effect	Weekly treatment (DTX[b]25 mg/m^2)		P	Triweekly treatment (DTX[b]75 mg/m^2)		P
	Study group (n=69)	Control group (n=35)		Study group (n=21)	Control group (n=37)	
Neutropenia	28 (40.6%)	11 (31.4%)	0.362	7 (31.8%)	12 (33.3%)	0.944
Thrombocytopenia	9 (13.0%)	4 (11.4%)	1.000[a]	3 (13.6%)	6 (16.7%)	1.000[a]
Reduced hemoglobin	20 (29.0%)	9 (25.7%)	0.725	6 (27.3%)	11 (30.6%)	0.926
Lymphopenia	6 (8.7%)	5 (14.3%)	0.501[a]	4 (18.2%)	5(13.9%)	0.710[a]
Nausea and Vomiting	19 (27.5%)	8 (22.9%)	0.607	5 (22.7%)	10 (27.8%)	0.788
Diarrhea	8 (11.6%)	5 (14.3%)	0.757[a]	4 (18.2%)	4 (11.1%)	0.443[a]
Muscle pain	7 (10.1%)	9 (25.7%)	0.038	3 (13.6%)	6 (16.7%)	1.000[a]
Fatigue	33 (47.8%)	18 (51.4%)	0.728	12 (54.5%)	16 (44.4%)	0.309
Excitement or Insomnia	12 (17.4%)	13 (37.1%)	0.026	5 (22.75)	8 (22.2%)	1.000[a]
Fluid retention	7 (10.1%)	5 (14.3%)	0.532[a]	1 (4.5%)	4 (11.1%)	0.644[a]
Stomach burning sensation or Abdominal pain	15 (21.7%)	12 (34.3%)	0.168	4 (18.2%)	9 (24.3%)	0.751[a]

a: Fisher's exact test; b: docetaxel

patient receives weekly treatment or triweekly treatment of docetaxel. To determine whether the patient's age could affect the incidence rate of HSR, we compared HSR incidences between the patients in the control group and study group within two age groups (≥65 and <65). The rate of HSR in these two age groups did not differ significantly between the control group and study group. After excluding the possible effect of docetaxel treatment strategy and patient age on the incidence of HSR, our result has showed that a regular dose of dexamethasone premedication in the control group does not have an advantage over a low dose of dexamethasone in the study group in terms of preventing docetaxel induced HSRs. As for the adverse effects, the hematologic toxicity did not differ significantly between two groups of patients regardless whether they received weekly or triweekly treatment. However, for those receiving weekly treatment of docetaxel, the rate of lymphopenia in the control group was 14.7% (5/35), which was slightly higher than that in the study group (8.6%, 6/69), even though the difference was not statistically significant. Since most patients were only followed up for two treatment cycles, the statistic analysis of the long-term side effects of dexamethasone might be biased. The small sample number in the control group might also have affected the statistic result. Results from more control patients are needed for further analysis. Similarly, among patients receiving weekly docetaxel treatment, the incidence rates of muscle pain and excitement/insomnia in the control group were higher than those in the study group (P=0.038, P=0.026). However, these significant differences did not exist in patients receiving triweekly docetaxel treatment. Although possible interactions between docetaxel and other medications cannot be ruled out, the difference between weekly and triweekly treated patients might be due to the side effects caused by prolonged 3 times a week oral dexamethasone treatment (David and Scott, 2013; Kellokumpu-Lehtinen *et al*., 2013). Overall, we believe that premedication with a low dose of dexamethasone is better than the current standard dosage. The current dexamethasone premedication needs further investigations because the side effects caused by dexamethasone may affect the efficacy of treatment.

CONCLUSION

In summary, by comparing the incidence of hypersensitivity reactions and other adverse effects in docetaxel treated patients receiving low a dose dexamethasone and those receiving the standard dose dexamethasone, we believe that using a reduced dosage of dexamethasone premedication is an effective and safe way for the prevention of docetaxel caused hypersensitivity and can be widely applied in clinics.

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