—Regular Articles—

Preventive Effects of Low-dose Dexamethasone for Delayed Adverse Events Induced by Carboplatin-based Combination Chemotherapy

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We performed a retrospective study to examine the protective effect of low-dose dexamethasone (DEX) on delayed adverse events induced by carboplatin (CBDCA)-based combination chemotherapy in patients with thoracic tumors. Low-dose DEX (4–8 mg/day) was administered on day 1 and after, in addition to a serotonin 5-HT_3 receptor antagonist. The acute adverse events (day 1) were well controlled in the patients with or without co-treatment of DEX. On the other hand, the delayed nausea, emesis, anorexia, and fatigue after day 2 failed to be controlled by 5-HT_3 antagonist alone. Co-treatment with DEX significantly suppressed the grade of the delayed adverse events during days 2–10. The mean ratio of complete protection during days 2–10 were significantly higher in the DEX-treated group compared with the non-DEX-treated group. These results reveal that low-dose DEX is a clinically effective treatment for the prevention of delayed adverse events induced by CBDCA-based combination chemotherapy.

Key words——carboplatin; nausea; dexamethasone; chemotherapy; adverse event

INTRODUCTION

Despite the use of antiemetics, the prevention of adverse events induced by chemotherapy is still unsatisfactory and delayed nausea and emesis, in particular, remain as clinically significant problems.[1,2] In the late 1990s, several professional organizations such as the Multinational Association of Supportive Care in Cancer, the National Comprehensive Cancer Network, and the American Society of Clinical Oncology, convened antiemetic guideline groups and published the findings of these expert panels.[3–7] Each of these documents was based on analyses of the available published trials and provided nearly identical recommendations. The emetic risk of chemotherapeutic agents is usually classified into 4 categories: High, moderate, low, and minimal.[3,4] The platinum chemotherapeutic agents, cisplatin (CDDP) and carboplatin (CBDCA) are categorized in high (emesis risk $>$90% without antiemetics) and in moderate (emesis risk 30–90% without antiemetics), respectively.[3,4]

The physiological mechanisms underlying nausea and emesis are considered to be different at the acute phase, occurring within 24 hours after chemotherapy, and the delayed phase, occurring 24 hours to several days after chemotherapy. Serotonin 5-HT_3 receptor antagonist is definitely recommended against acute nausea and emesis because serotonin plays a main role at the acute phase. On the other hand, the mechanism at the delayed phase is poorly understood.[6,8] Therefore several anti-emetic treatments are advocated: Dexamethasone (DEX), 5-HT_3 antagonist, DEX+5-HT_3 antagonist, DEX+neurokinin-1 receptor antagonist, or metoclopramide.[3–5] 5-HT_3 antagonists are without doubt the most effective antiemetics against acute nausea and emesis.[3–7] But, more recent reviews or randomized trials have questioned the relative contribution of 5-HT_3 antagonist alone for the prevention of delayed nausea and emesis.[4,9–12] DEX is considered to be effective antiemetic against acute or delayed nausea and emesis,[3] although the mechanisms by which steroids exert their antiemetic activity are not fully understood. However, these evidences have been extensively obtained in high emetic risk chemotherapy using CDDP. There is little information in moderate risk chemotherapy using CBDCA.[3–5] In addition, the op-

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timal dose of DEX for delayed nausea and emesis induced by chemotherapy have not been defined so far.[4]

Therefore, the purpose of this study was to assess the impact of DEX for the prevention of delayed adverse events induced by CBDCA-based combination chemotherapy.

METHODS

Subjects and Study Design Seventeen Japanese inpatients with thoracic tumors underwent tri-weekly CBDCA-based combination chemotherapy and participated in monitoring the adverse events[13] in Kagawa University Hospital between April 2005 and September 2006. The characteristics of the subjects are shown in Table 1. After obtaining written informed consent, patients conducted the adverse events monitoring using two support tools (Table 2) modified from the basis of Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) Japanese translated edition[14] by Japan Clinical Oncology Group/Japan Society of Clinical Oncology during the first 10 days after chemotherapy.[13] The grade of subjective symptoms scored by patients were checked by pharmacists to meet the above criteria[14] when they visited the bedside. Subjects meeting any of the following criteria were excluded from this study: 1) Complications inducing nausea and/or emesis (*e.g.*,

Table 1. Patient Characteristics

	DEX group	Non-DEX group	*p*-value
Number of patients	7	10	
Age (years)			
Median (range)	67 (38—72)	65 (54—82)	N.S.
Sex			
Male	6	6	N.S.
Female	1	4	
ECOG performance status			
0	6	9	N.S.
1	1	1	
Disease			
SCLC	2	5	
NSCLC	4	4	N.S.
Thymic cancer	1	1	
Prior chemotherapy			
Yes	5	5	N.S.
No	2	5	
CBDCA dose (target *AUC*) [a]			
Median (range)	4.8 (3.8—5.5)	4.5 (3.5—5.5)	N.S.
VP-16 dose (mg/m^2) [b]			
Median (range)	90 (80—100)	100 (80—100)	N.S.
DOC dose (mg/m^2) [c]			
Median (range)	60 (60)	60 (60)	N.S.
DEX dose (mg/day)			
Median (range)	6 (4—8)	—	
DEX duration (days)			
Median (range)	5.0 (4—9)	—	
5-HT$_3$ duration (days) [d]			
Median (range)	5.0 (4—9)	6.5 (3—12)	N.S.

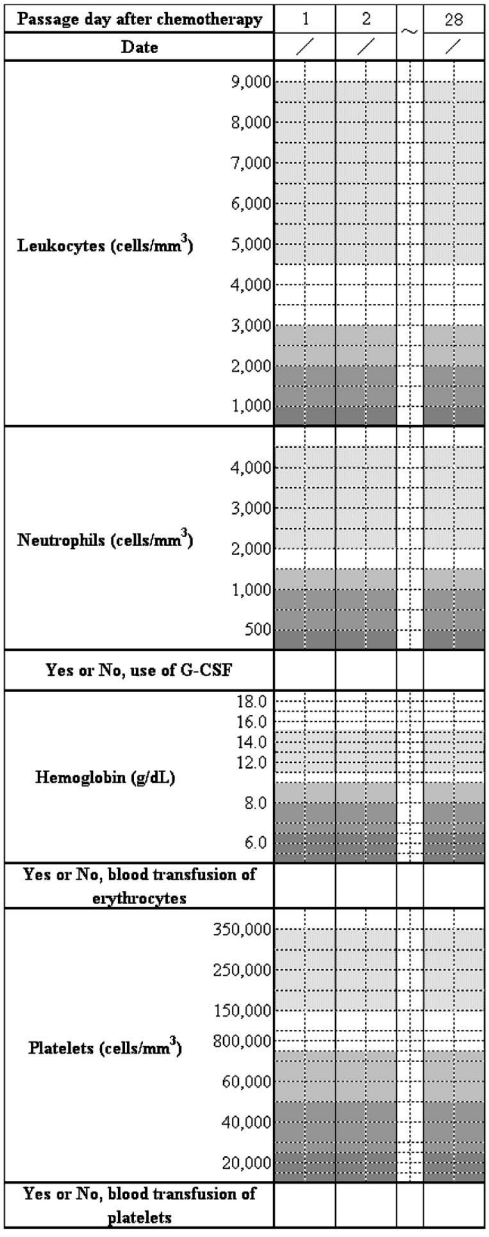
ECOG: Eastern Cooperative Oncology Group, SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer, CBDCA: carboplatin, *AUC*: area under the concentration *versus* time curve (mg·min/ml), VP-16: etoposide, DOC: docetaxel, DEX: dexamethasone, 5-HT$_3$: serotonin receptor antagonist, N.S.: not significant. *a*) The dose of CBDCA for each patient was determined with Calvert's formula by using individual creatinine clearance (CCr) values: dose (mg) = target *AUC*·(CCr + 25), *b*) As combination with CBDCA (day 1), VP-16 (days 1–3) was selected for SCLC, *c*) As combination with CBDCA (day 1), DOC (day 1) was selected for NSCLC and thymic cancer, *d*) 5-HT$_3$ was administered as the maximum dose of the package insert in Japan (*i.e.*, ondansetron and ramosetron were administered 4 mg and 0.3 mg, until twice a day, respectively).

Table 2. Two Support Tools for Adverse Events Monitoring

A

Passage day after chemotherapy			1	2	～	28
Date			/	/		/
Fatigue	3	Severe fatigue interfering with activities of daily living	3	3		3
	2	Moderate fatigue causing difficulty with some activities of daily living	2	2		2
	1	Mild fatigue, but no interference with activities of daily living	1	1		1
	0	No particular symptoms	0	0		0
Anorexia	3	No appetite or association with significant weight loss; Intravenous drip indicated	3	3		3
	2	Little appetite or oral intake alteration without significant weight loss	2	2		2
	1	Loss of appetite without alteration in eating habits	1	1		1
	0	No particular symptoms	0	0		0
Nausea	3	Severe nausea associated with significant weight loss; Intravenous drip necessary	3	3		3
	2	Moderate nausea or oral intake decrease without significant weight loss	2	2		2
	1	Mild nausea or loss of appetite without alteration in eating habits	1	1		1
	0	No particular symptoms	0	0		0
Stomatitis	3	Severe symptoms or impossible oral intake	3	3		3
	2	Moderate symptoms, but possible oral intake if modified diet	2	2		2
	1	Mild symptoms without alteration in normal diet	1	1		1
	0	No particular symptoms	0	0		0
Neuropathy	3	Severe symptoms interfering with activities of daily living	3	3		3
	2	Moderate symptoms interfering with function, but no interference with activities of daily living	2	2		2
	1	Mild symptoms including tingling, but no interference with function	1	1		1
	0	No particular symptoms	0	0		0
State of stool			Constipation Regular Diarrhea	Constipation Regular Diarrhea		Constipation Regular Diarrhea
Diarrhea frequency						
Emesis frequency						

B



G-CSF: Granulocyte-Colony Stimulating Factor. One scored the points of subjective symptoms by patients, and the other recorded objective symptoms by pharmacists, as shown in (A) and (B), respectively. A: the intensity range of each adverse event was grade 0–3. Grade 4, which is disabled activities of daily living, and grade 5, which is death induced by adverse event, were rarely occurred in clinical and they were excluded as it was considered that the patient can not continue to monitor adverse events in those state. B: the intensity range of each adverse event was grade 0–4 and the intensity of each adverse event and criteria range were indicated by the background coloring. The criterion range corresponds to women in this hospital.

symptomatic brain metastases, ulcerative diseases, and severe hepatic dysfunction *etc.*); 2) use of drugs which affect nausea and/or emesis during investigation period, except for antiemetic (*e.g.*, major or minor tranquilizers, corticosteroids for any other reason *etc.*); 3) concomitant radiotherapy during investigation period. DEX at the median (range) dose of 6 mg/day (4–8 mg/day) was intravenously administered to the patients on day 1 and after, in addition to 5-HT_3 antagonist. If a patient suffers from nausea and emesis despite the use of antiemetics, metoclopramide (10 mg/body) is intravenously administered.

This study was approved by the Institutional Review Board of Kagawa University Hospital.

Statistical Analysis Comparison between DEX-

treated group and non-DEX-treated control group was carried out by the following methods: The patient characteristics were analyzed using Chi-square tests, Fisher's exact test, and Student's *t*-test, as appropriate. The grade of each adverse event was analyzed using Mann-Whitney's *U*-test every day and during days 2–10. Complete protection against each adverse event was defined as the absence of more than grade 1.[12,15] The ratio of complete protection against acute each adverse event (day 1) was analyzed using Fisher's exact test, and the mean ratio of complete protection against delayed each adverse event (during days 2–10) was analyzed using Student's *t*-test and Welch's *t*-test, as appropriate. All *p*-values were two-tailed and $p<0.05$ was considered significant.

RESULTS

On day 1 nausea and emesis were well controlled in both the DEX-treated and the non-DEX-treated groups (Fig. 1). Emesis was completely protective and only nausea of grade 1 was seen in 20% subjects. On the other hand, there was a difference between both groups in frequency and grade of nausea and emesis after day 2. The grades of nausea and emesis during days 2–10 were significantly lower in the DEX-treated group compared with the non-DEX-treated

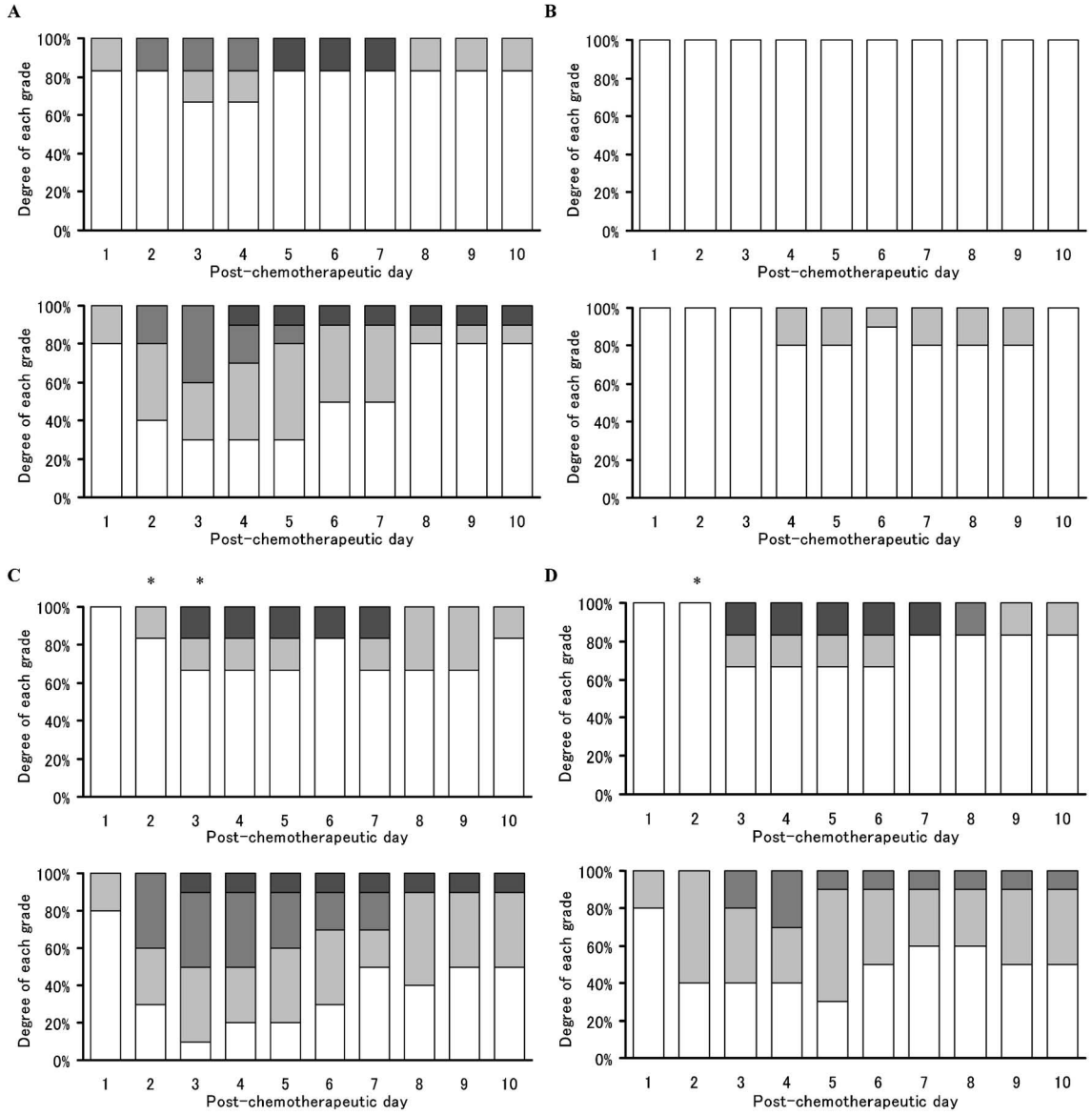


Fig. 1. Preventive Effects of Dexamethasone for Nausea (A), Emesis (B), Anorexia (C), and Fatigue (D) Induced by Carboplatin-based Combination Chemotherapy

Upper side: DEX-treated group, Lower side: non-DEX-treated group. □: grade 0, ▒: grade 1, ▓: grade 2, ■: grade 3. *$p<0.05$.

group ($p<0.01$). The mean ratio of complete protection against nausea and emesis during days 2–10 in the DEX–treated group was 82.5±2.1% and 100±0% (mean±S.E.), respectively, which were significantly higher ($p<0.01$) in comparison with the non-DEX-treated group (52.2±7.4% and 87.8±3.2%, respectively).

As well as nausea and emesis, anorexia and fatigue were well controlled on day 1, but not after day 2 in non-DEX-treated group (Fig. 1). The grades of anorexia and fatigue during days 2–10 were significantly lower in the DEX-treated group compared with the non-DEX-treated group ($p<0.01$). The mean ratio of complete protection against anorexia and fatigue during days 2–10 in the DEX-treated group was 71.4±3.4% and 76.2±5.3%, respectively, which were significantly higher ($p<0.01$) in comparison with the non-DEX-treated group (33.3±5.0% and 46.7±3.3%, respectively). These adverse events gradually disappeared after day 10 in both groups.

Stomatitis, peripheral neuropathy, constipation, and diarrhea were well controlled and no severe adverse event (grade 4 and 5) was seen in both groups through the observation period. In addition, there was no characteristic difference between both groups in the myelosuppression nadir of leukocytes, neutrophils, hemoglobin, and platelets.

DISCUSSION

The platinum chemotherapeutic agents, CDDP and CBDCA are a key drug for lung cancer, gynecologic cancer, and other malignancies. As a result of having considered insufficient renal function in elderly patients,[16–21] CBDCA was selected, but not CDDP. There was little information on the optimal dose of DEX for preventing the delayed nausea and emesis induced by CBDCA. This study shows that concomitant treatment of low-dose (4–8 mg/day) DEX with 5-HT_3 antagonist was effective for the delayed adverse events induced by CBDCA-based combination chemotherapy.

It is well-known that the presence of acute nausea and emesis is the main prognostic factor for delayed them. It goes without saying that the best way to prevent delayed nausea and emesis is to control acute them.[12] Serotonin plays a main role in acute nausea and emesis induced by chemotherapy. In fact, the acute nausea and emesis were well controlled in the non-DEX-treated group the same as in the DEX-treated group (Fig. 1). However, more recent reviews or randomized trials have questioned the relative contribution of 5-HT_3 antagonist alone for the prevention of delayed nausea and emesis.[4,9–12] In our results (Fig. 1), the treatment with 5-HT_3 antagonist alone (non-DEX-treated group) was less effective for the delayed nausea and emesis on days 2–10. Therefore, we should reconsider the routine administration of 5-HT_3 antagonist alone for delayed nausea and emesis induced by CBDCA categorized in the moderate emetic risk, although it was recommended in the guidelines.[3–5]

DEX is considered to be an effective antiemetic agent at both acute and delayed phase,[3] although its mechanism is not fully understood. In the guidelines, the recommended dose of DEX co-administrated with 5-HT_3 antagonist for acute nausea and emesis in high and moderate emetic risk chemotherapy is 20 mg/day and 8 mg/day, respectively, whereas the optimal dose of DEX for delayed these events has not been defined so far.[4] Recently DEX at a dose of 8 mg/day was reported to be effective to delayed nausea and emesis induced by moderate emetic risk chemotherapy using other than platinum agents, cyclophosphamide, doxorubicin, epirubicin, adriamicin, and irinotecan.[12,15,22] Therefore, we determined the maximum dose of DEX to be 8 mg/day and decreased the dose properly depending on CBDCA dose. As a result, the co-administration of DEX at the dose of 4–8 mg/day (median; 6 mg/day) with 5-HT_3 antagonist well controlled the delayed nausea and emesis induced by CBDCA-based combination chemotherapy compared to 5-HT_3 antagonist alone (Fig. 1). DEX also prevented the delayed anorexia and fatigue (Fig. 1), which is in line with the results of Inoue et al. when irinotecan was used for chemotherapy.[22] In addition, the co-treatment with low-dose DEX was well tolerated. Therefore, such a low dose of DEX is recommended for preventing these delayed adverse events induced by CBDCA-based combination chemotherapy, although higher dose of DEX is needed in CDDP.[3–6]

We should be careful when interpreting the results of this small retrospective study; however, our result revealed that low-dose DEX with 5-HT_3 antagonist was a clinically effective treatment for the prevention of delayed nausea, emesis, anorexia, and fatigue induced by CBDCA-based combination chemotherapy.

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