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ORIGINAL ARTICLE

Weekly paclitaxel in patients with recurrent or metastatic head and neck cancer

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Abstract
Purpose To evaluate the efficacy and safety of weekly paclitaxel in patients with recurrent or metastatic head and neck cancer (HNC) by combined analysis of early and late phase II trials.
Methods Eligibility criteria included histologically proven HNC with recurrent or metastatic disease, measurable disease, PS 0-2, and one or no prior chemotherapy regimens. Treatment consisted of a 1-h infusion of paclitaxel at a dose of 100 mg/m^2 weekly for 6 weeks of a 7-week cycle. A total of 74 patients were enrolled: 37 between February and November 2004 in an early phase II trial and 37 between October 2005 and July 2006 in a late phase II trial.
Results The median number of treatment cycles was two, and median dose intensity was 84.2 mg/m^2/week. The most common grade 3–4 adverse events were leukopenia (37.5%), neutropenia (30.6%), anemia (12.5%), constipation (8.3%), peripheral neuropathy (5.6%), anorexia (5.6%), and pneumonitis (5.6%). Overall response rate was 29.0% according to RECIST. The median duration of response, median time to progression, and median survival time were 7.4, 3.4, and 14.3 months, respectively.
Conclusions This study demonstrates that weekly paclitaxel has promising activity with acceptable toxicity in the treatment of recurrent or metastatic HNC.

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Keywords Paclitaxel · Head and neck cancer · Phase II study · Weekly infusion

Introduction

Head and necks cancers (HNCs) are the sixth most common cancers worldwide, and approximately 500,000 new cases are projected annually [22]. An estimated 60% of these patients present with locally advanced disease (stage III/IV) [32]. Although the treatment of these locally advanced HNC has progressed, half will recur. While some of these are suitable for salvage treatment, including surgery or chemoradiotherapy, most are scheduled to receive palliative chemotherapy only.

Platinum-based combination chemotherapy is widely used as first-line treatment for recurrent/metastatic HNC. However, while several randomized trials have suggested that combination chemotherapy yields superior response rates, it is also associated with increased toxicity and no significant survival advantage over single agent chemotherapy [1, 4, 5, 15, 31, 35]. A recent randomized trial of platinum-based chemotherapy with or without cetuximab demonstrated significant survival benefit in the arm receiving cetuximab [30]. However, cetuximab was not given to patients in the control arm at the time of progression and it therefore remains unanswered whether the addition of cetuximab to first-line chemotherapy provides a survival benefit over sequential use of platinum-based chemotherapy followed by cetuximab at the time of progression. In other words, standard therapy in first-line treatment for recurrent/metastatic HNC has not yet been established. Furthermore, treatment options for patients who are refractory to platinum-based chemotherapy are limited. Optimal treatment options for these patients are therefore desirable.

Paclitaxel is a novel diterpenoid isolated from the bark of the Pacific yew, *Taxus brevifolia* [34]. Paclitaxel has high-affinity binding to microtubules, promotes microtubule assembly, and stabilizes tubulin polymers against depolymerization affecting cells in the G2/M-phase [24, 26].

Previous studies of high-dose tri-weekly paclitaxel (200–250 mg/m^2) in patients with advanced or recurrent/metastatic HNC demonstrated treatment activity, with an overall response of 35–40%, but that this regimen was associated with severe neuropathy and myelosuppression [6, 27]. Since the survival of patients with recurrent or metastatic HNC is limited, additional consideration should be given to their quality of life.

Previous studies of weekly paclitaxel at a reduced single dose for other cancers demonstrated comparable efficacy to a high-dose tri-weekly regimen with milder toxicities, including neuropathy and myelosuppression [28].

At the time the present trials were planned, only one prospective phase II study of weekly paclitaxel in the treatment of recurrent or metastatic HNC had appeared. Results showed acceptable toxicities but the poor response rate of 9.3% (4/43) [3]. Thus, no data were available to support the practical use of weekly paclitaxel in the treatment of recurrent or metastatic HNC, albeit that weekly paclitaxel has been widely used in the treatment of HNC patients who are refractory to a platinum-based chemotherapy.

Here, therefore, we conducted two multicenter, phase II trials, an early and late phase II trial of weekly paclitaxel in patients with recurrent or metastatic HNC, to evaluate efficacy and safety in the two trials and to confirm data on safety and efficacy between them.

Patients and methods

The subjects of the present study were patients enrolled in two multicenter trials, an early and a late phase II trial of weekly paclitaxel in the treatment of recurrent or metastatic HNC. To allow the safety and efficacy of these trials to be compared, they were conducted under the same design. Each trial was conducted at 19 institutions in Japan.

Eligibility criteria included histologically or cytologically proven HNC with recurrent or metastatic disease; age 20 years or older but less than 75; a measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; adequate organ function, as defined by an absolute neutrophil count (ANC) >2,000/μL, platelet count >100,000/μL, hemoglobin >9.0 g/dL, AST <100 IU/L, ALT <100 IU/L, total bilirubin <1.5 mg/dL, and serum creatinine <1.5 mg/dL; and life expectancy >2 months from the beginning of treatment. Patients were excluded if they had received two or more prior regimens of chemotherapy for recurrent/metastatic HNC. The study protocol was reviewed and approved by the ethics committee of each of the participating institutions before patient enrollment began. Informed consent was obtained from all patients.

Treatment

On the basis of the results of a phase I trial of weekly paclitaxel in solid tumors [20], patients in both the early and late phase trials received a 1-h iv infusion of paclitaxel at a dose of 100 mg/m^2 weekly over a 7-week cycle on days 1, 8, 15, 22, 29, and 36, followed by 2 weeks of rest until unacceptable toxicity, patient refusal, or disease progression were observed. Patients received premedication with 8 mg dexamethasone (iv), 50 mg ranitidine (iv),

and 50 mg diphenhydramine hydrochloride (po) 30–60 min prior to paclitaxel infusion.

Dose modification of paclitaxel by 20 mg/m^2 was allowed if a patient experienced any of the following adverse events: (1) febrile neutropenia, (2) grade 3 or 4 thrombocytopenia, (3) grade 3 or 4 non-hematological toxicity, (4) grade 2 or higher peripheral neuropathy or myalgia/arthralgia, or (5) any toxicity that caused a dose to be skipped or required a dose reduction at the discretion of the physician. Dose reduction to less than 60 mg/m^2 was not allowed.

Study endpoints

The primary endpoints in each trial were safety and response rate as assessed by WHO criteria, which could be compared to historical data. Secondary endpoints were duration of response, response rate based on the response evaluation criteria in solid tumors (RECIST), median time to progression (TTP), and median survival time (MST). The response rates and adverse events were evaluated by an independent safety and efficacy assessment committee. Responses were assessed by CT and/or MRI scans every 4 weeks. Adverse events were evaluated every week according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0. A subject's TTP was defined as the time from the date of the enrollment in the present study to the first documentation of disease progression, subsequent therapy, or death. The duration of response was defined as the time from the date of the first confirmation of response to the first documentation of disease progression.

Statistical design

To confirm safety and efficacy, applications for approval of anti-neoplastic drugs in Japan typically require two studies conducted under the identical design, an early and a late phase II trial. If the early trial does not demonstrate promising activity, the late trial is withheld. In each of the present studies, the expected response rate was considered to be 25% and the threshold response rate was set at 10%. Thirty-six patients were needed to evaluate efficacy in each study in order to reject the hypothesis that the true efficacy rate was below the threshold response rate, giving $\alpha = 0.025$ (one-sided) and $\beta = 0.3$. A survival curve was estimated using the Kaplan–Meier method [16]. In the present trials, safety and efficacy analyses were conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of paclitaxel. All statistical analyses were carried out using SAS Version 8.2.

Results

Patient characteristics

A total of 74 patients were enrolled, 37 between February and November 2004 in the early phase II trial and 37 between October 2005 and July 2006 in the late phase II trial. The two trials had one patient each who did not receive any administration of paclitaxel due to PS 3 or ANC <2,000/μL. Patient characteristics are shown in Table 1. Of note, a total of 25 (34.7%) patients had advanced cancer, 47 (65.3%) had recurrent cancer, and 62 (86.1%) had a prior history of chemotherapy, including platinum-based chemotherapy (76.4%). Of these, 23 (31%) had received prior platinum-based chemotherapy for recurrent/metastatic disease. No relevant differences in patient characteristics were observed between individuals in the early and late phase trial groups.

Treatment administration

For both the early and late phase trials, the combined median number of treatment cycles was 2.0 (range 1–10) and the median number of doses was 12 (range 1–50). The combined median interval between cycles was 14.0 days (range 13–28 days), and the median dose intensity was 84.2 mg/m^2/week (range 43.0–107.7 mg/m^2/week).

Safety

The safety evaluation was conducted in 72 patients who received at least one dose of paclitaxel. Adverse events are shown in Table 2. The most common grade 3–4 non-hematological adverse events were constipation (8.3%), peripheral neuropathy (5.6%), anorexia (5.6%), and pneumonitis (5.6%), while grade 3–4 hematological adverse events were leukopenia (37.5%), neutropenia (30.6%), and anemia (12.5%). No deaths related to paclitaxel treatment were seen during the study period. The incidence of greater than grade 2 peripheral neuropathy was 25.0% (18/72).

The percentage of patients requiring dose reductions was 34.7% (25/72). Although 16.7% (12/72) of patients required cessation of therapy, only 5.6% (4/72) was unable to complete the protocol of at least one cycle of paclitaxel. The most common reason for cessation was peripheral neuropathy, seen in 6.9% (5/72) of patients. The median time to onset of peripheral neuropathy was 34 days (range 1–141), and the median dose of onset was 500 mg/m^2 (range 100–1600 mg/m^2). In those patients who experienced peripheral neuropathy, 14.5% (8/55) recovered, 7.3% (4/55) remitted, and 78.2% (43/55) failed to recover by the end of the protocol.

Table 1 Patient characteristics

Characteristics	Number of subjects (%)		
	Total, $n = 72$	Early phase II study, $n = 36$	Late phase II study, $n = 36$
Sex			
Male	56 (77.8)	30 (83.3)	26 (72.2)
Female	16 (22.2)	6 (16.7)	10 (27.8)
Age			
Median age (range)	61 (41–74)	60.5 (44–74)	62.5 (41–74)
P.S. (ECOG)			
0	48 (66.7)	22 (61.1)	26 (72.2)
1	22 (30.6)	13 (36.1)	9 (25.0)
2	2 (2.8)	1 (2.8)	1 (2.8)
Disease status			
Advanced	25 (34.7)	10 (27.8)	15 (41.7)
Recurrent	47 (65.3)	26 (72.2)	21 (58.3)
Histopathological diagnosis			
Squamous cell carcinoma	61 (84.7)	32 (88.9)	29 (80.6)
Adenoid cystic carcinoma	4 (5.6)	1 (2.8)	3 (8.3)
Others	7 (9.7)	3 (8.3)	4 (11.1)
Primary lesion			
Oral cavity	8 (11.1)	8 (22.2)	0
Paranasal cavity	8 (11.1)	3 (8.3)	5 (13.9)
Nasopharynx	8 (11.1)	4 (11.1)	4 (11.1)
Oropharynx	12 (16.7)	6 (16.7)	6 (16.7)
Hypopharynx	18 (25.0)	7 (19.4)	11 (30.6)
Larynx	6 (8.3)	3 (8.3)	3 (8.3)
Salivary gland	7 (9.7)	1 (2.8)	6 (16.7)
Others	5 (6.9)	4 (11.1)	1 (2.8)
Prior treatment			
Chemotherapy*	62 (86.1)	32 (88.9)	30 (83.3)
Cisplatin-based chemotherapy	55 (76.4)	29 (80.6)	26 (72.2)
Others	7 (9.7)	3 (8.3)	4 (11.1)
Surgery	36 (50.0)	20 (55.6)	16 (44.4)
Radiotherapy	60 (83.3)	30 (83.3)	30 (83.3)

PS performance status, *ECOG* Eastern Cooperative Oncology Group

* Including adjuvant chemotherapy, neoadjuvant chemotherapy, and chemoradiotherapy

Efficacy

Thirty-six patients in each study were assessed for efficacy (Table 3). Overall response rates (RRs) in the early and late trial were 33.3% (95% CI: 18.6, 51.0%) and 36.1% (95% CI: 20.8, 53.8%), respectively. In combined analysis of two trials, RR according to WHO and RECIST criteria were 34.7% (95% CI: 23.9, 46.9%) and 29.0% (95% CI: 18.7, 41.2%), respectively. RR according to the WHO criteria in the 55 patients who received prior platinum-based chemotherapy was 32.7% and 30.4% in the 23 patients who received prior platinum-based chemotherapy for recurrent/metastatic disease (Table 4). RR in the 60 patients who received prior radiotherapy, including adjuvant therapy, neoadjuvant therapy, and chemoradiotherapy, was 30.0 and 58.3% in the 12 patients who did not receive prior radiotherapy.

The median duration of response was 8.5 months (95% CI: 5.4, 11.5 months) in the early trial, 6.9 months (95% CI: 3.2, 7.9 months) in the late trial, and 7.4 months (95% CI: 5.4, 9.4 months) in total.

The median follow-up period in all patients was 13.8 months (range: 1.6-33.8 months). Median TTP and MST were 3.4 months (95% CI: 3.0, 4.6 months; Fig. 1) and 14.3 months (95% CI: 11.0, 19.4 months; Fig. 2), respectively. In the 64 patients excluding those with nasopharyngeal cancer, median TTP and MST were 3.2 months (95% CI: 2.9, 4.3 months) and 13.0 months

Table 2 Adverse events

	Total ($n = 72$)				Early phase II study ($n = 36$)				Late phase II study ($n = 36$)			
	≥Grade 1		≥Grade 3		≥Grade 1		≥Grade 3		≥Grade 1		≥Grade 3	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Nausea	22	30.6	2	2.8	9	25.0	1	2.8	13	36.1	1	2.8
Anorexia	19	26.4	4	5.6	10	27.8	1	2.8	9	25	3	8.3
Constipation	22	30.6	6	8.3	10	27.8	5	13.9	12	33.3	1	2.8
Fatigue	47	65.3	2	2.8	25	69.4	1	2.8	22	61.1	1	2.8
Peripheral neuropathy	55	76.4	4	5.6	27	75.0	1	2.8	28	77.8	3	8.3
Pneumonitis	8	11.1	4	5.6	5	13.9	3	8.3	3	8.3	1	2.8
Alopecia	68	94.4			34	94.4			34	94.4		
Rash	28	38.9			15	41.7			13	36.1		
ALT	25	34.7			17	47.2			8	22.2		
Leukopenia	65	90.3	27	37.5	32	88.9	13	36.1	33	91.7	14	38.9
Neutropenia	60	83.3	22	30.6	29	80.6	13	36.1	31	86.1	9	25.0
Anemia	59	81.9	9	12.5	29	80.6	3	8.3	30	83.3	6	16.7
Thrombocytopenia	7	9.7			6	16.7			1	2.8		

ALT alanine aminotransferase

Table 3 Response according to WHO and RECIST criteria

Criteria	Study	Number of patients						RR (%)	95% CI
		Assessable patients	CR	PR	NC/SD	PD	NE		
WHO	Total	72	5	20	23	18	6	34.7	23.9, 46.9
	Early	36	2	10	9	11	4	33.3	18.6, 51.0
	Late	36	3	10	14	7	2	36.1	20.8, 53.8
RECIST	Total	69	4	16	33	9	7	29.0	18.7, 41.2
	Early	35	2	7	15	7	4	25.7	12.5, 43.3
	Late	34	2	9	18	2	3	32.4	17.4, 50.5

CR complete response, *PR* partial response, *NC* no change, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *CI* confidence interval, *WHO* World Health Organization, *RECIST* response evaluation criteria in solid tumors

(95% CI: 9.9, 16.9 months), respectively. As 11 patients (15.3%) had non-squamous cell carcinomas histology, which included 4 with adenoid cystic carcinoma and 7 with either mucoepidermoid tumor, adenocarcinoma, poorly differentiated carcinoma, acinar cell carcinoma, carcinoma, large cell carcinoma, or undifferentiated carcinoma, MST was also determined excluding these patients. MST was 13.4 months in the 61 patients with squamous cell carcinomas and 11.7 months in the 45 patients with squamous cell carcinomas of the oral cavity, paranasal cavity, oropharynx, hypopharynx, and larynx cancer. In the 23 patients who had received prior platinum-based chemotherapy for recurrent/metastatic disease, median TTP and MST were 3.2 months (95% CI: 2.5, 6.7 months) and 11.4 months (95% CI: 7.4, 19.4 months), respectively.

Discussion

Here, we conducted early and late phase II trials of weekly paclitaxel in patients with recurrent or metastatic HNC. Results demonstrated comparable safety and efficacy between the two trials. Further, the combined RR of the two trials was comparable to those previously reported in studies of tri-weekly paclitaxel in patients with advanced or recurrent HNC [6, 27]. All adverse events that occurred in the two trials were manageable, and no treatment-related deaths were observed. Although most patients had received prior chemotherapy, MST was 14.3 months, which was superior to that of previous studies in first-line patients with recurrent or metastatic HNC.

Of interest, MST in the 64 patients excluding those with nasopharyngeal cancer and in the 23 who had received

Table 4 Response rates according to patient characteristics (WHO)

Characteristic	Number of patients					RR (%)
	CR	PR	NC	PD	NE	
Sex						
Male	3	16	19	14	4	33.9
Female	2	4	4	4	2	37.5
Age (Years)						
<65	4	12	12	16	6	32.0
≥65	1	8	11	2		40.9
Histopathological diagnosis						
Squamous cell carcinoma	3	16	21	16	5	31.1
Adenoid cystic carcinoma		1	1	2		25.0
Others	2	3	1		1	71.4
Primary lesion						
Oral cavity		4	1	2	1	50.0
Nasal cavity				1		0
Paranasal cavity	1	2	4	1		37.5
Maxillary sinus				1		0
Nasopharynx	1	3	3		1	50.0
Oropharynx	1	4	3	4		41.7
Hypopharynx	1	4	8	3	2	27.8
Larynx		1	2	2	1	16.7
Salivary gland	1	2	1	2	1	42.9
Tympanum			1			0
External auditory canal				2		0
Prior radiotherapy						
None		7	1	3	1	58.3
Radiotherapy*	5	13	22	15	5	30.0
Prior chemotherapy						
None	1	3	3	2	1	40.0
Cisplatin-based chemotherapy	4	14	17	16	4	32.7
Others		3	3		1	42.9

CR complete response, *PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *WHO* World Health Organization

* Including adjuvant therapy, neoadjuvant therapy, and chemoradiotherapy

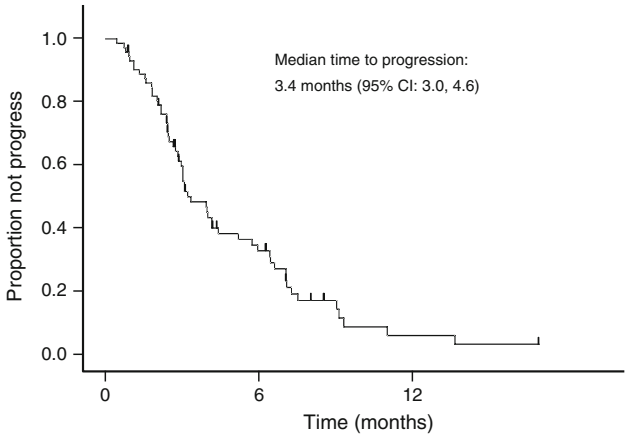

Fig. 1 Combined time to progression from the early and late phase II studies. The median time to progression was 3.4 months (95% CI: 3.0, 4.6 months)

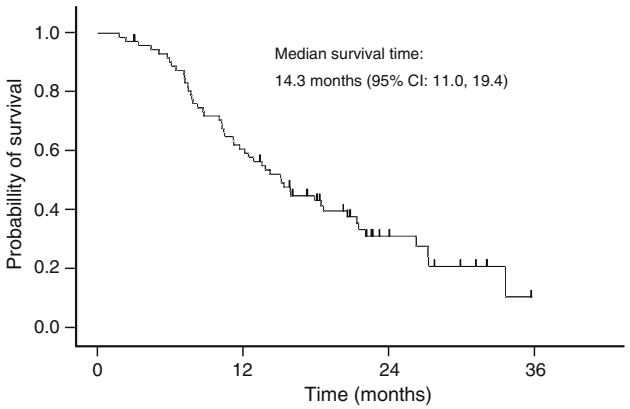

Fig. 2 Combined overall survival from the early and late phase II studies. The median follow-up time of patients for overall survival was 13.8 months, with a median overall survival time of 14.3 months (95% CI: 11.0, 19.4 months)

prior platinum-based chemotherapy for recurrent/metastatic disease was 13.0 and 11.4 months, respectively. Allowing for the fact that this was a nonrandomized trial with a relatively small number of patients, these results are nevertheless better than those in the previous studies, particularly in showing that weekly paclitaxel was active in the treatment of HNC whether patients had received prior platinum-based chemotherapy or not.

Recently, the addition of cetuximab to platinum-based chemotherapy was shown to significantly prolong overall survival without exacerbating chemotherapy-associated toxicity or quality of life in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) [10]. Furthermore, the addition of cetuximab to paclitaxel was also shown to exert promising activity in a first-line setting of a phase II trial, which had an RR of 71% and a complete response rate of 20%. Weekly paclitaxel might therefore be a good alternative to platinum-based chemotherapy for first-line patients with recurrent or metastatic SCCHN.

Treatment options for patients with recurrent or metastatic HNC who are refractory to platinum-based chemotherapy are limited. Several second-line chemotherapy regimens with cytotoxic agents, including methotrexate, vinorelbine, bleomycin, docetaxel, and S-1, have been investigated in the treatment of patients with recurrent or metastatic HNC after previous platinum-based chemotherapy [7, 11–14, 36]. Response rates and MST in these studies were 10–46.2% and less than 5 months, respectively, and it has accordingly not been possible to draw definitive conclusions on their clinical benefit.

Recently, a single institutional prospective study of weekly paclitaxel (80 mg/m^2, weekly, 6 consecutive weeks) in SCCHN patients in whom platinum-based chemotherapy failed demonstrated a response rate of 43.3% and MST of 8.5 months [9]. Although this rate is superior to that of the present study, the study was conducted at a single institution and had no independent safety and efficacy assessment committee, while our study was a multicenter trial with independent safety and efficacy assessment committees. Further, our present study demonstrated a better duration of response and survival, which might be associated with the higher dose of paclitaxel in the present study.

A combined analysis of second-line use of cetuximab with or without platinum-based chemotherapy for patients with recurrent/metastatic SCCHN in whom platinum-based chemotherapy failed concluded that cetuximab would be effective as monotherapy and could be considered a therapeutic option [29]. However, the response rate, median TTP and MST of cetuximab alone in these patients were 13%, 2.3, and 5.9 months, respectively, indicating the need for further optimization of treatment options.

Although the number of patients who had previously received platinum-based chemotherapy for recurrent/metastatic disease in the present study was small, weekly paclitaxel showed a superior response rate and survival to that of previously reported agents and may therefore also be promising in second-line treatment following cisplatin-based regimens. Recently, weekly taxane-based chemotherapy was shown to exhibit promising activity as an induction chemotherapy in the primary therapy setting [17, 25, 33], suggesting that this dose-dense strategy may be particularly applicable to sequential treatment programs for HNC.

Long-term administration of weekly paclitaxel increases the incidence and severity of peripheral neuropathy, which often reduces quality of life. In our present patients who experienced peripheral neuropathy, 14.5% recovered and 7.3% remitted, while 78.2% failed to recover by the end of the protocol. Such sustained peripheral neuropathy may be limiting for patients receiving longer-term palliative therapy. Several studies have investigated anti-neuropathy drugs, including amifostine, gabapentin, and vitamin E, but all failed to demonstrate any benefit for these patients [2, 8, 18, 19, 21, 23]. The development of effective anti-neuropathy drugs is desirable.

Several limitations of the present study warrant mention. First, subjects included eight patients with nasopharyngeal cancer, which is considered to carry a better prognosis than other HNCs. Second, subjects included chemo-naive patients and patients who had not been confirmed to be refractory to platinum-based chemotherapy. Third, the present trials were nonrandomized, and differences in patient populations due to selection bias may have influenced outcomes and toxicity rates and thereby limit comparisons between studies. Fourth, the study included a range of histological subtypes. In other words, the subjects represented a markedly heterogeneous population.

In summary, this study demonstrated that weekly paclitaxel has promising activity with acceptable toxicity in the treatment of recurrent or metastatic HNC. Paclitaxel may be a good treatment option for recurrent or metastatic HNC.

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