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ORIGINAL ARTICLE

Triweekly reduced-dose docetaxel combined with cisplatin in recurrent/metastatic head and neck squamous cell carcinoma: a multicenter phase II study

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Abstract
Purpose To test the efficacy and safety of a triweekly reduced-dose docetaxel (60 mg/m^2) regimen combined with a standard dose of cisplatin in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).
Patients and methods Patients with R/M HNSCC were enrolled. All eligible patients received intravenous docetaxel 60 mg/m^2 combined with cisplatin 75 mg/m^2 on day 1 and then every 3 weeks thereafter. Treatment was continued until disease progression, patient intolerance, or death.
Results In total, 58 patients were enrolled and 41 patients were evaluated. Among the evaluated population, one patient achieved a complete response (2.4%) and nine patients achieved a partial response (22%), resulting in an overall response rate of 24.4%. Furthermore, 17 patients had stable disease (41.5%), which corresponds to a disease control rate of 65.9%. With a median follow-up of 24 months (1–43 months), progression-free survival was 170 days (95% confidence interval 97.9–242.1) and the median overall survival was 265 days (95% confidence interval 89.0–441.0) in evaluable population. The most common toxicities (≥grade III) were leucopenia (66.7%) and anemia (33.3%).
Conclusions Triweekly reduced-dose docetaxel 60 mg/m^2 combined with cisplatin is effective and feasible for Taiwanese patients with R/M HNSCC. However, the hematologic toxicity of this regimen should be carefully monitored and managed.

Keywords Head and neck squamous cell carcinoma · Docetaxel · Recurrent · Metastatic

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Introduction

Head and neck squamous cell carcinoma (HNSCC), which arises from the mucosa of the upper aerodigestive tract including the oral cavity, oropharynx, hypopharynx, and larynx, is ranked the sixth most common type of cancer in the world [1] and the fourth leading cause of male cancer death in Taiwan [2]. Unfortunately, treatment is likely to fail in more than 70% of patients, with locoregional recurrence occurring in about 60% and metastatic disease developing in as many as 30% of patients with primary HNSCC [3]. The prognosis of patients with recurrent/metastatic (R/M) HNSCC is poor, with median survival ranging from 6 to 9 months irrespective of the type of conventional chemotherapy used [4–6]. Many chemotherapy regimens have been evaluated, and although most have shown adequate treatment response, few have been reported to improve survival, with the exception of regimens that include cetuximab, an IgG1 monoclonal antibody that inhibits ligand binding to EGFR [7, 8].

Docetaxel, a microtubule-stabilizing agent, has been demonstrated to be effective in locally advanced as well as R/M HNSCC [9–23]. Several phase II studies have evaluated the value of docetaxel in the treatment of R/M HNSCC. Single-agent docetaxel administered as first-line treatment at a dose of 100 mg/m^2 triweekly or 40 mg/m^2 weekly has been reported to result in a response rate ranging from 21 to 42% [11–14]. When docetaxel was combined with nonplatinum cytotoxic agents, such as 5-FU [15, 16], gemcitabine [17], or topotecan [18], the toxicity increased without any significant improvement in treatment response. In contrast, the response rates have been shown to be significantly higher when docetaxel was combined with platinum-based cytotoxic agents. Studies have shown that a triweekly schedule consisting of docetaxel 100 mg/m^2 or 75 mg/m^2 combined with cisplatin 75 mg/m^2 results in response rates ranging from 33 to 53% [19–22]. In addition, Samlowski et al. [23] showed that triweekly schedule consisting of docetaxel 65 mg/m^2 combined with carboplatin achieved a 25% overall response rate. The major toxicity concern with such combination regimens is severe ($\geq$grade III) in neutropenia, with the incidence in most of those studies being more than 50% [22]. Few studies, however, have investigated the efficacy and safety of a reduced dose of docetaxel–cisplatin combination thereapy. One such study showed that weekly cisplatin 25 mg/m^2 and docetaxel 35 mg/m^2 resulted in a good response rate (42%) and acceptable toxicity (10%) [24]. As mentioned earlier, finding an approach that reduces hematologic toxicity without affecting treatment response seems to be the most important issue when using docetaxel–platinum combination chemotherapy for R/M HNSCC.

Large variability in the pharmacokinetics and pharmacodynamics of docetaxel treatment between patients has been observed and studied for some time [25]. Studies have shown that cases of docetaxel-induced myelosuppression are more severe in Asian populations than in other ethnic populations, prompting researchers in Asian countries to administer docetaxel at reduced dosages for the treatment of cancer. For example, in a study conducted in Japan, Sekinea et al. reduced the dose of docetaxel by 20% without changing the dose of cisplatin for the treatment of advanced non-small cell lung cancer. They found no differences in response, survival, or grade III/IV toxicities when compared with studies in Western countries [26]. In another Japanese study, Kojima et al. [27] found that reducing the weekly dose of docetaxel from 36 to 30 mg/m^2 did not influence the effectiveness of the regimen in patients with hormone-refractory advanced prostate cancer. It seems that dose modification in Asian populations treated with docetaxel is both feasible and reasonable. Based on concerns about docetaxel-induced myelosuppression, especially in Asian patients with R/M HNSCC, we conducted this phase II trial in an Asian population to see whether a reduced dose of docetaxel combined with a standard dose of cisplatin would result in a comparable response rate and an acceptable level of side effects.

Patients and methods

Study design

The protocol for this open-label, noncomparative phase II study aimed at evaluating the effectiveness and tolerability of triweekly reduced-dose docetaxel and cisplatin as first-line chemotherapy for the treatment of R/M HNSCC was approved by the Institutional Review Board of the Taipei Veterans General Hospital (No.93-04-03). The primary end point was to determine overall response, progression-free survival, overall survival, and disease control rate; a safety profile was also collected and used as the secondary end point. The sample size was calculated based on the two-stage design by Simon et al. [28]. The treatment program was designed with a refuse response rate of 20% (P0) and to provide a significance level of 0.05 (α) with a statistical power of 80% ($\beta = 0.2$) when assessing the activity of the regimen at a 40% response rate (P1). Thus, the first step was planned to include 13 patients; if > 3 patients' responses were recorded, the study would enroll an additional 28 patients, up to a total number of 41 patients.

Eligibility

The enrolled patients had histologically confirmed nonnasopharyngeal HNSCC with locoregional recurrence after curative local treatment and were either unsuitable for

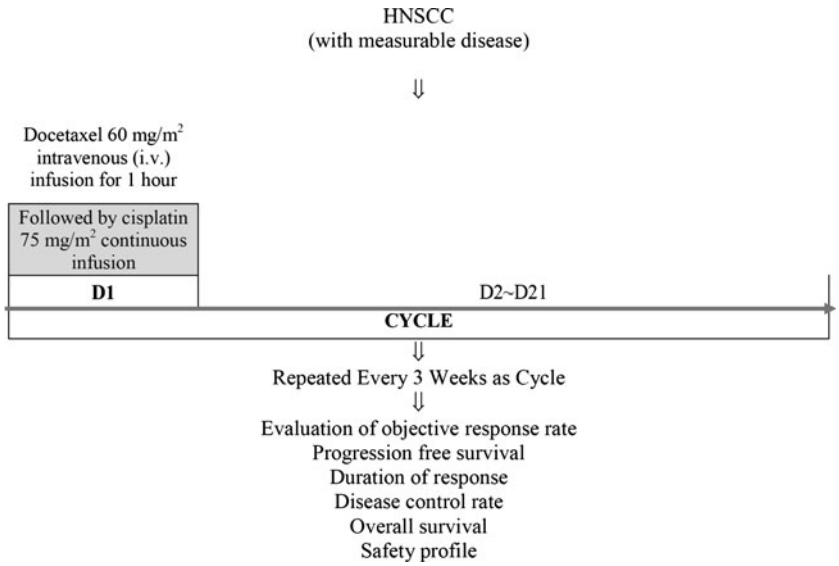

Fig. 1 Algorithm of the triweekly cisplatin/docetaxel treatment

further local treatment or had primary distant metastasis. Only patients aged between 20 and 75 years with radiological evidence of measurable (>2 cm) lesions were eligible for the study. Other entry criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, a life expectancy of at least 12 weeks, an absolute neutrophil count (ANC) $\geq$ 1,500/μl, a platelet count (PLT) $\geq$ 75,000/μl, a creatinine clearance (CCR, estimated by Cockroft-Gault Formula) $\geq$ 50 ml/min, and a total bilirubin less than 1.5 times the upper limit of normal range. Before study entry, all patients were required to provide written informed consent to the protocol.

The exclusion criteria included the presence of CNS metastasis, the presence of any other malignancy with the exception of nonmelanoma skin cancer or cervical carcinoma in situ prior to the entry of study, the presence of bone-only metastasis, the use of previous primary chemotherapy for R/M disease, previous treatment with docetaxel, the presence of an active noncontrolled infection, or the presence of a medical problem unrelated to the malignancy that would limit full compliance with the study or expose the patient to extreme risk.

Treatment plan

Within 14 days of the beginning of treatment, patients underwent a complete evaluation including computed tomography scanning or magnetic resonance imaging of the head and neck region, endoscopic examination, chest X-ray, abdominal sonography, and laboratory tests including a complete blood cell count, serum chemistry, and urinalysis. The treatment scheme is shown in Fig. 1. Docetaxel (TYXAN@, TTY Biopharm Co., Ltd.) 60 mg/m^2 i.v. infusion for 1 h followed by cisplatin 75 mg/m^2 i.v. continuous infusion for 24 h were administered on day 1 and every 3 weeks thereafter in a cycle. We used the 24-h infusion of cisplatin because of its lesser emetogenicity and comparable effectiveness in treating of R/M HNSCC [29, 30]. Treatment was administered until disease progression, intolerable toxicity, or consent withdrawal.

Dose modification

Dose modification was based on the worst degree of toxicity. Toxicity level was graded according to the common toxicity criteria (CTC) established by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program, version 3, 2003. If $\geq$grade II toxicity was noted, immediate treatment interruption would be followed by a selective dose reduction depending on the type of toxicity as described later; this was continued until recovery to at least grade I toxicity: If febrile neutropenia $\geq$38.5°C, absolute neutrophil count (ANC) <500/mm^3, or platelet count $<2.5 \times 10^4$/mm^3 developed but resolved within 1 week, a 75% dose of docetaxel would be given during the remaining cycles. Treatment would be stopped completely if no recovery occurred within 2 weeks. If grade II neurologic toxicities developed, the treatment would be delayed until there was evidence of $\leq$grade I toxicity within 2 weeks, after which a 75% dose of docetaxel would be given during the remaining cycles. Treatment would be discontinued if severe ($\geq$grade III) neurologic toxicities occurred. The cisplatin dose was adjusted to 50% if the estimated creatinine clearance was $\leq$50 ml/min but >40 ml/min. Cisplatin would be withheld for a maximum of 2 weeks if the estimated creatinine clearance was $\leq$40 ml/min.

Efficacy and safety assessment

The overall response rate was defined as the sum of the proportions of patients graded as having complete remission or partial remission, these having been confirmed by repeated assessment. Response was evaluated according to the proposal for response evaluation criteria in solid tumors (RECIST) criteria [31]. Tumor assessment was performed at the end of the 3rd cycle of chemotherapy, and this was repeated for every 3 cycles until withdrawal from the study. The severity of any toxicity was graded and reported using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3, 2003. Toxicity assessment was examined before treatment and then repeated every week during each cycle until the patient left the study.

Statistical analysis

All analyses were carried out using SPSS 14.0 (SPSS, Inc., Chicago, IL, USA). OS was defined as the time elapsed between the date of registration of study and the date of death or last appearance. PFS was defined as the time between the date of study entry and the date of documented progression, last follow-up or death due to any cause. Median and life tables were computed using the product-limit estimate by the Kaplan–Meier method, and the log-rank test was applied for comparison of the survival periods between groups. The response analysis of each clinical factor was compared using the chi-square or Fisher's exact test for the category variables. Two-sided P values less than 0.05 were considered statistically significant.

Results

Patient characteristics

From March 2005 to October 2008, 58 patients were recruited in both the intention-to-treat (ITT) and the safety populations. Among the ITT population, median body surface area was 1.61/m^2 (1.26–2.28/m^2). Overall, 17 patients were not considered for evaluation for the following reasons: 8 patients withdrew early due to intolerable adverse effects, although they are all less than grade IV (Supplementary Table 1); 3 with physicians' incompliance to study protocol, and one with patients' incompliance to receiving regular treatment and examination; 3 patients received less than 3 cycles of treatment before progression; and 2 patients died before the first evaluation. In the end, 41 patients were evaluated in this study. There was only one woman in the evaluated population (2.4%). The most common primary tumor sites were oral cavity (37.0%) and the hypopharynx (35.2%). Other relevant patient characteristics are shown in Table 1.

Analysis of efficacy

As shown in Table 2, the overall response rate was 24.4% ($n = 10$), which included one patient who achieved a complete response (2.4%) and nine patients who achieved a partial response (22%). Overall, 17 patients had stable disease (41.5%), which corresponds to a disease control rate of 65.9%. Only one patient among the ten patients who achieved a complete or partial response showed evidence of progressive disease before leaving the study. The median response duration was 105 days. The median progression-free survival was 170 days (95% CI 97.9–242.1) versus 123 days (95% CI 50.4–195.6), and the overall survival was 265 days (95% CI 89.0–441.0) versus 199 days (95% CI 113.7–284.3) for EP versus ITT (Fig. 2). The one-year survival rate was 17.1% among the evaluated population.

Safety evaluation

Extent of exposure

In the intention-to-treat population, the mean cycle of exposure to docetaxel was 4.14 ± 0.32. For each cycle

Table 1 Summary of the demographic characteristics of the intention-to-treat (ITT; $n = 58$) and evaluable population (EP; $n = 41$)

Demographic characteristics	Summary statistics	
Age (years)		
N	ITT; $n = 58$	EP; $n = 41$
Median (IQR)	54.5 (10.75)	52.1 (13.91)
Min–Max	36–75	36–75
Gender		
Male (%)	57 (98.3)	41 (100)
Female (%)	1 (1.7)	0 (0)
Min–Max	1.3–2.3	1.4–2.2
ECOG performance		
0 (%)	9 (15.5)	5 (12.2)
1 (%)	41 (70.7)	32 (78.0)
2 (%)	8 (13.8)	4 (9.8)
Primary tumor site		
Larynx (%)	5 (8.6)	5 (12.2)
Oral cavity (%)	20 (34.5)	9 (22.0)
Oropharynx (%)	9 (15.5)	5 (12.2)
Hypopharynx (%)	19 (32.8)	17 (41.5)
Other (%)	5 (8.6)	5 (12.2)
Previous treatment for HNSCC		
Tumor resection (%)	36 (69.2)	23 (56.0)
Radiotherapy (%)	47 (90.4)	33 (80.5)
Chemotherapy (%)	39 (75.0)	27 (65.9)

N number, *IQR* inter-quartile range, *Min* minimal, *Max* maximal, and *HNSCC* head and neck squamous cell carcinoma

Table 2 Summary of responses among the population evaluated ($n = 41$)

Objective Response	The first-stage EP ($n = 13$)	Total EP ($n = 41$)
CR	1 (7.7%)	1 (2.4%)
PR	3 (23.1%)	9 (22.0%)
SD	4 (30.8%)	17 (41.5%)
PD	5 (38.5%)	14 (34.1%)

EP evaluable population, *CR* complete response, *PR* partial response, *SD* stable disease, and *PD* progressive disease

dose, docetaxel and cisplatin showed good protocol compliance for the median (IQR) doses of 60 (7.5) mg/m^2 and 75 (4.69) mg/m^2, respectively. The median cumulative doses of docetaxel and cisplatin were 180 and 225 mg/m^2, respectively. Details are shown in Table 3.

Summary of adverse events

The most common severe toxicities (≥grade III) among the safety population were leucopenia (66.7%), anemia (33.3%), and anorexia (22.3%). Other severe acute toxicities are shown in Table 4. There were two deaths in this study, and both were due to septic shock as a result of grade V leucopenia. The first one was a 68-year-old man with a local recurrent oral SCC. He suffered from grade IV leucopenia after first course of study medications, and grade III pneumonia developed 8 days after treatment. Unfortunately, the condition deteriorated to grade V sepsis even with broad-spectrum antibiotics and finally the patient passed away. The second case was a 51-year-old man with hypopharyngeal SCC with multiple distant metastases. He was also a victim of chronic diabetes. He suffered from grade IV leucopenia 7 days after receiving his third course of study medications. The condition deteriorated rapidly to grade V leucopenia and finally the patient passed away. Common grade I/II toxicities (data not shown) included mucositis (25.9%), constipation (44.8%), diarrhea (34.5%), nausea (55.1%), insomnia (34.5%), and alopecia (31.0%). These findings are generally consistent with those previously reported for docetaxel and/or cisplatin. Symptomatic deterioration without objective evidence of disease progression was noted in 7 cases, which resulted in the discontinuation of treatment.

Discussion

In this phase II study, the overall response rate to a triweekly reduced-dose docetaxel–cisplatin regimen was 24.4%, which is similar to that achieved in previous studies on docetaxel monotherapy for the treatment of R/M HNSCC

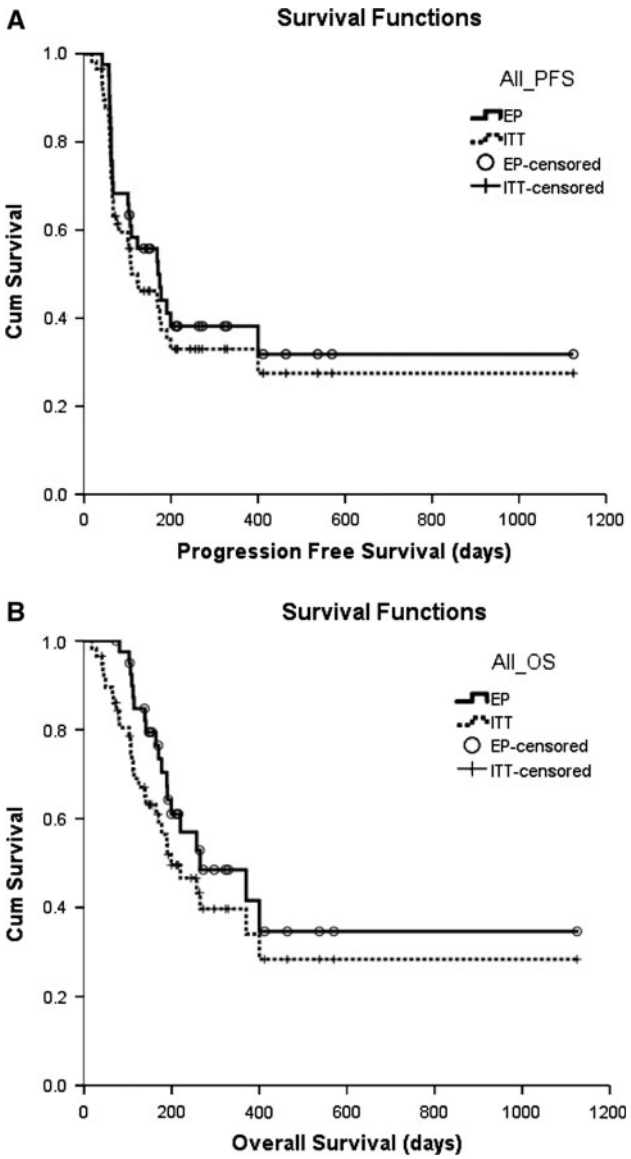

Fig. 2 Survival analysis of patients in the study. **a** Kaplan–Meier survival curve of progression-free survival (median 170 days [95% CI 97.9–242.1] versus 123 days [95% CI 50.4–195.6]) in the evaluated population ($n = 41$) versus intention-to-treat population ($n = 58$). **b** Kaplan–Meier survival curve of overall survival (median 265 days [95% CI 89.0–441.0] versus 199 days [95% CI 113.7–284.3]) in the evaluated population ($n = 41$) versus intention-to-treat population ($n = 58$)

[11–14]. Although the response rate may seem to be inferior to the rates reported in other studies on docetaxel–cisplatin combination therapy [19–22], the progression-free survival and overall survival rates in our study do not differ significantly from those reported previously [19–22]. The relatively high survival rate might be attributed to the high rate of disease control (65.9%) among patients with stable disease (41.5%). This is an interesting finding and suggests that further studies are needed in this area.

Table 3 Extent of exposure among the intention-to-treat population ($n = 58$)

Extent of exposure	Docetaxel ($n = 58$)	Cisplatin ($n = 58$)
Cycle number		
Mean (SE)	4.14 (0.32)	4.12 (0.52)
Median (IQR)	3.00 (4.00)	3.00 (4.00)
Min–Max	1.00–10.00	1.00–10.00
Cycle dose		
Mean (SE)	56.30 (0.64)	70.25 (1.20)
Median (IQR)	60.00 (7.50)	75.00 (4.69)
Min–Max	46.67–60.00	41.67–75.00

SE standard error, *IQR* inter-quartile range, *Min* minimal, and *Max* maximal

Table 4 Incidence of severe (≥grade III) toxicities among the safety population ($n = 58$)

Toxicity	Grade	
	III (%)	IV (%)
Asthenia	1 (1.9%)	0 (0%)
Anorexia	11 (20.4%)	1 (1.9%)
Pain	3 (5.6%)	0 (0%)
Nausea	1 (1.9%)	0 (0%)
Vomiting	6 (11.1%)	0 (0%)
Diarrhea	1 (1.9%)	1 (1.9%)
Fever	2 (3.7%)	0 (0%)
Hemorrhage	2 (3.7%)	3 (5.6%)
Anemia	15 (27.8%)	3 (5.6%)
Leucopenia	16 (29.6%)	20 (37.0%)*
Thrombocytopenia	3 (5.6%)	2 (3.7%)
Hypokalemia	4 (7.4%)	2 (3.7%)
Hyponatremia	6 (11.1%)	1 (1.9%)
SGOT increased	2 (3.7%)	0 (0%)
SGPT increased	2 (3.7%)	1 (1.9%)
Weight loss	1 (1.9%)	0 (0%)
Cough	1 (1.9%)	0 (0%)

SGOT serum glutamyl oxaloacetic transaminase, *SGPT* serum glutamyl pyruvic transaminase

* Two patients suffered from grade IV leucopenia and died; this was recorded as grade V leucopenia

Myelosuppression is the most common docetaxel-induced toxicity, especially among Asian populations [33]. In Caucasians, the most commonly recommend dose of docetaxel in a triweekly reduced-dose docetaxel–cisplatin regimen is 75 mg/m^2 [19–22, 34]. In Japanese, however, the maximum tolerated dose is 70 mg/m^2 and the recommended dose is 60 mg/m^2 [32]. In the current study, the dosage of docetaxel was reduced due to severe myelosuppression caused by docetaxel 75 mg/m^2/cisplatin 75 mg/m^2 in our pilot study: two male patients (65-year-old and 37-year-old) with good performance (ECOG PS 1) and without systemic diseases developed severe myelosuppression, and the second one progressed to grade V leucopenia with septic shock and death. In these two cases as well as two deaths in the evaluable population, myelotoxicity of docetaxel in R/M HNSCC may be attributed to the poor general condition of patients, since two patients were elder and another two men had a poor nutritional status (body mass index = 16.9) and chronic diabetes individually, although these conditions were not reflected in their performance status scores. Despite the use of a lower dose of docetaxel in Japan and in this study, the incidence of leucopenia is still high, with ≥grade III leukopenia being observed in 66.7% of patients, which is similar to the incidence of severe leucopenia due to docetaxel 75 mg/m^2 combined with cisplatin 75 mg/m^2 in Western countries. One possible explanation for this ethnic difference is genetic variation in the cytochrome P450 (CYP) 3A4 system between the different races. Docetaxel is mainly cleared by hepatic metabolism, which utilizes the CYP3A4 system of the liver. Hor et al. analyzed the relationship between the transcriptional regulators of CYP3A and ABCB1, pharmacokinetics and pharmacodynamics, and three ethnic groups. The results indicated that although the degree of docetaxel-induced myelosuppression was greater among Chinese patients than among other two races, genotypic variability could not completely account for the difference [35]. Another possible explanation is that the clearance of docetaxel is significantly decreased as the body surface area decreases [36], which may account for the higher toxicity in Asian populations. However, the detailed mechanisms underlying the ethnic differences in docetaxel-related myelosuppression are still unclear, and further in-depth studies are needed.

In conclusion, this phase II trial showed that triweekly reduced-dose docetaxel is a feasible regimen for treating R/M HNSCC in Taiwanese patients. The general condition and ethnic difference that affect the recommended docetaxel dosage need to be emphasized, at least when treating R/M HNSCC. In the cisplatin/docetaxel setting, the hematologic toxicity should be carefully monitored and managed even in the reduced-dose docetaxel–cisplatin regimen. A further study designed to reduce the incidence of myelosuppression without decreasing the effectiveness of the docetaxel-cisplatin treatment, which might involve adjusting the dose of cisplatin, changing the frequency of docetaxel administration, or adding inhibitors of EGFR signaling, such as Cetuximab, are warranted.

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