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ORIGINAL ARTICLE

Phase II trial of combination treatment with paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CSPOR-HN02)

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Background: The standard of care for first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) is combination treatment with platinum, 5-FU and cetuximab (PFE). However, this regimen requires hospitalization to ensure proper hydration and continuous infusion of 5-FU, and causes severe nausea and anorexia. We evaluated the efficacy and safety of paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with R/M SCCHN.

Patients and methods: Eligibility criteria included recurrent and/or metastatic, histologically proven SCC of the oropharynx, oral cavity, hypopharynx or larynx; PS 0-1; adequate organ function; no suitable local therapy for R/M SCCHN; and no prior systemic chemotherapy for R/M SCCHN. Chemotherapy consisted of paclitaxel 100 mg/m^2 on days 1, 8; carboplatin area under the blood concentration-time curve 2.5 on days 1, 8, repeated every 3 weeks for up to 6 cycles; and cetuximab at an initial dose of 400 mg/m^2, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicities. Primary end point was overall response rate. Secondary end points were safety, treatment completion rate, progression-free survival, overall survival, and clinical benefit rate. Planned sample size was 45 patients.

Results: Forty-seven subjects were accrued from July 2013 to October 2014. Of 45 evaluable, 40 were male; median age was 63 years; Eastern Cooperative Oncology Group Performance Status was 0/1 in 23/22 cases; site was the hypopharynx/oropharynx/oral cavity/larynx in 17/11/10/7 cases; and 36/9 cases were smokers/nonsmokers, respectively. Overall response rate, the primary end point, was 40%. Median overall survival was 14.7 months and progression-free survival was 5.2 months. Grade 3/4 adverse events included neutropenia (68%), skin reaction (15%), fatigue (9%) and febrile neutropenia (9%). A potentially treatment-related death occurred in one patient with intestinal pneumonia.

Conclusions: The PCE regimen shows promising activity with acceptable toxicity in the outpatient clinic. Further studies are needed to compare PCE with PFE in this population.

Registered clinical trial number: UMIN000010507.

Key words: paclitaxel, carboplatin, cetuximab, squamous cell carcinoma of the head and neck

Introduction

Head and neck cancers (HNCs) are the sixth-most common cancer in the world, and approximately 500 000 new cases are projected annually [1]. An estimated 60% of these patients present with locally advanced disease (stage III/IV). Although treatment of locally advanced HNC has progressed, half of cases still recur. Some of these patients are eligible for salvage treatment, including surgery or chemoradiotherapy, but most receive palliative chemotherapy.

In the EXTREME study [2], the addition of cetuximab to platinum plus 5-FU (PF) demonstrated significantly improved survival over PF alone, and combination treatment with PF and cetuximab (PFE) is now considered to be the standard regimen for first-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) [3, 4]. However, this regimen had 82% rate of grade 3 or 4 toxicity. Furthermore, it is associated with a number of problematic toxicities, including mucositis, anorexia, fatigue, nephrotoxicity and ototoxicity, which lead to a worsening of the patient's quality of life. Although adequate supportive care, including the use of subcutaneously implanted 'PORT' catheters, can allow administration of PFE in the outpatient clinic, most patients require hospitalization to ensure proper hydration and continuous infusion of 5-FU.

The prognosis for R/M SCCHN is limited. Ideally, the goal of treatment is to extend survival while ensuring good quality of life. Thus, a more appropriate regimen which avoids worsening the patient's quality of life is clearly required.

In a previous study for R/M SCCHN patients who received platinum derivatives, combination of paclitaxel, carboplatin and cetuximab (PCE) demonstrated manageable and well tolerable safety profile with promising clinical activity, with a response rate of 56% and median time to progression of 5 months [5]. Although various PCE schedules are commonly used in daily clinical practice, little prospective data is available.

Here, we conducted a phase II study to evaluate the efficacy and safety of PCE as first-line treatment of R/M SCCHN.

Patients and methods

Eligibility criteria

Key eligibility criteria included histologically proven SCCHN; primary lesion located in the larynx, oropharynx, hypopharynx or oral cavity; measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; no suitable local therapy for R/M disease; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1; age 20 years or older; adequate organ function; life expectancy of at least 3 months; no prior chemotherapy except for that given >6 months previously as curative therapy; no prior systemic chemotherapy for R/M disease; and written informed consent. Key exclusion criteria included previous systemic chemotherapy for R/M SCCHN (unless part of multimodality treatment of locoregionally advanced SCCHN completed >6 months before study entry); surgery (except diagnostic biopsy) or radiotherapy within 4 weeks before study entry; simultaneous or metachronous double cancers except carcinoma in situ or intramucosal tumor within 5 years before study entry, and symptomatic central nervous system metastases; severe myelosupression and infection; lung fibrosis, acute lung damage and intestinal lung disease; and prior cetuximab or anti-epidermal growth factor receptor (EGFR) treatment.

The study protocol was approved by the ethics committee at each participating center. The trial was conducted in accordance with the Declaration of Helsinki; all patients provided written informed consent before study entry. This trial was registered at the UMIN Clinical Trials Registry as UMIN000010507.

Study treatment

Chemotherapy consisted of paclitaxel 100 mg/m^2 on days 1, 8; carboplatin area under the blood concentration-time curve (AUC) 2.5 on days 1, 8, repeated every 3 weeks for up to 6 cycles; and cetuximab at an initial dose of 400 mg/m^2, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicities (supplementary Figure S1, available at *Annals of Oncology* online). Doses of chemotherapy were modified in cases of severe hematological or non-hematological toxicity (supplementary methods, available at *Annals of Oncology* online).

Assessment

Tumor responses were assessed by computed tomography or magnetic resonance imaging at baseline and at 8-week intervals after the start of treatment until disease progression or treatment discontinuation. ORR was assessed by independent central review, including two radiologists, and evaluated using RECIST version 1.1. Adverse events were monitored weekly throughout the study and evaluated using Common Terminology Criteria for Adverse Events version 4.0. After the completion of study treatment, disease progression, survival status and any further anticancer treatments were documented at follow-up visits every 6 months.

Design and statistics

The study was conducted under a single-arm, multicenter, phase II design to evaluate the safety and efficacy of PCE as first-line treatment of R/M SCCHN. Primary end point was overall response rate (ORR) based on RECIST version 1.1 [6]. Secondary end points included safety, treatment completion rate, progression-free survival (PFS), overall survival (OS), and clinical benefit rate. The primary objective of the study was to establish the proof-of-concept for PCE by evaluating ORR. For this, we assumed that the ORR of PFE is 40%, based on the EXTREME study, and the purpose of the study was to determine whether the observed ORR of PCE was more than 40% minus 5% (which was 35%). The target accrual to assure the probability of observing an ORR of PCE greater than 35% was therefore 40 patients.

Binominal confidence intervals (CIs) for ORR were estimated by the exact method. Survival curves were estimated using the Kaplan–Meier method [7]. Primary analyses were conducted on the full analysis set (FAS) population, defined as all registered patients, excluding those who were found to be ineligible after enrollment, did not receive any study treatment, or did not have any data for efficacy end points due to the events that are clearly unrelated to the protocol treatment. Safety analyses were done for all registered patients who received at least one dose of study treatment. All *P*-values are shown as two tailed. Statistical analyses were carried out using SAS version 9.4.

Results

Demographics and disposition

From July 2013 and October 2014, 47 subjects were accrued from 16 sites (Patient Flow Diagram, supplementary Figure S2, available at *Annals of Oncology* online). All patients were eligible and had study treatment while one patient discontinued due to depression and the other died from drowning in the bathroom, leading to no efficacy data for them. Thus, the FAS for efficacy

Table 1. Patient characteristics ($n = 45$)

Variable	Number of patients
Age (years), median (range)	63 (41–76)
<65	25
≥65	20
Sex	
Female	5
Male	40
PS	
0	23
1	22
Primary site	
Hypopharynx	17
Oropharynx	11
Oral cavity	10
Larynx	7
Extent of disease	
Only locoregionally recurrent	8
Metastatic with or without locoregional recurrence	37
Previous treatment	
Radiation	28
Chemotherapy	13
Postoperative chemoradiotherapy	4
Smoking history	
Smokers	36
Brinkman index, median (range)	735 (10–3680)
Nonsmokers	9

Table 2. Response ($n = 45$) on central review

Response	Number of patients (%)
Complete response	2 (4.4%)
Partial response	16 (35.6%)
Stable disease	9 (20.0%)
Progressive disease	16 (35.6%)
Not evaluable[a]	2 (4.4%)

[a]Due to adverse events related to the protocol treatment.

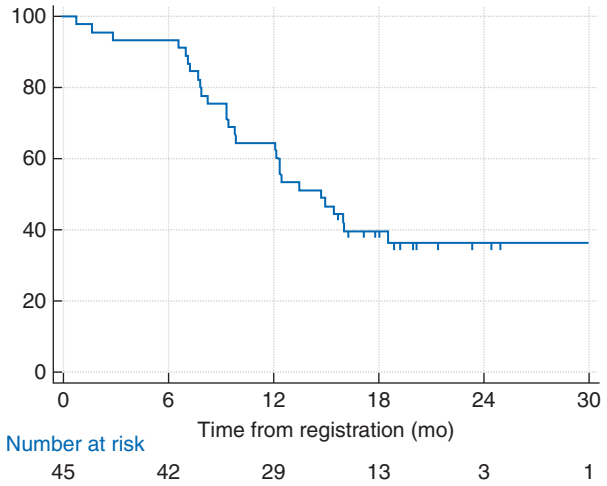

Figure 1. Overall survival.

analyses was consisted of 45 patients. Patient characteristics are presented in Table 1. There were 40/5 males/females with a median age 63 years (range, 41–76) and an ECOG PS 0/1 of 23/22 patients. Most common primary site was hypopharynx ($n = 17$). Of note, a total of 37 patients had distant metastases with or without locoregional recurrence, while 8 patients had locoregional recurrence alone. Seventeen patients had prior history of chemotherapy, including postoperative chemoradiotherapy ($n = 4$).

Efficacy

Forty-five patients were assessed for efficacy on central review (Table 2). ORR was 40.0% (95% CI, 25.7% to 55.7%), meaning that the study met its predefined criteria. Two (4.4%) patients achieved complete response, 16 (35.6%) partial response, and 9 (20%) stable disease, giving a clinical benefit rate of 60%. With a median follow-up of 20 months, median overall survival was 14.7 months (95% CI, 9.8–not reached) with observed death events of 28 (62%) (Figure 1). Median PFS was 5.2 months (95% CI, 3.9–5.6 months) (Figure 2). Forty-two patients discontinued study treatment due to disease progression ($n = 35$), death ($n = 3$) and adverse events ($n = 2$), patient refusal ($n = 1$) and others ($n = 2$). Five patients are still receiving cetuximab maintenance.

Adverse events

Adverse events occurring in 10% or more of patients are presented in Table 3. Grade 3–4 adverse events in 10% or more during PCE were neutropenia (68%) and skin reaction (15%), while those during cetuximab maintenance were rash acneiform (10%) and skin reaction (10%). One potentially treatment-related death occurred in one patient with intestinal pneumonia.

Treatment compliance

Median number of PCE cycles was 6. Sixteen (35.6%) patients completed 6 cycles of PCE and 29 (64.4%) received cetuximab monotherapy. Details of treatment compliance are listed in supplementary Table S1, available at *Annals of Oncology* online. Median duration of each study drug was 16.0 weeks for paclitaxel, 16.3 weeks for carboplatin, 22.1 weeks for cetuximab and 11.0 weeks for cetuximab monotherapy during the maintenance period. Median relative dose intensity of each study drug was 82.5% for paclitaxel, 82.5% for carboplatin, 93.3% for cetuximab, and 87.5% for cetuximab monotherapy during the maintenance period.

Subsequent treatment

Details of subsequent treatment are shown in supplementary Table S2, available at *Annals of Oncology* online. A total of 32 (68%) patients received subsequent treatment after the discontinuation of study treatment. Moreover, a total of 14 (31%) patients received third-line therapy. Of note, a total of nine

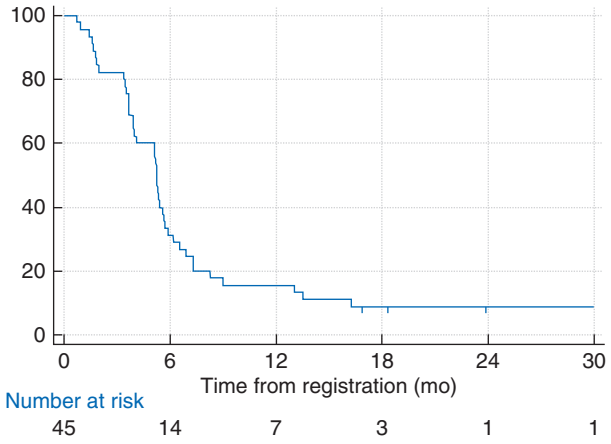

Figure 2. Progression-free survival.

patients (four second-line and five third-line) received immune checkpoint inhibitors, including anti-PD-1/PDL-1 antibody, in clinical trials.

Discussion

The results of this phase II study showed that PCE produces promising activity, with ORR of 40% in first-line treatment of R/M SCCHN. Toxicities were manageable and were tolerated in the outpatient clinic, with weekly adjustment of dosages according to toxicity. Moreover, this combination showed promising efficacy, with a median PFS of 5.2 months and median OS of 14.7 months. These findings suggest that further evaluation of PCE in a phase III trial is warranted.

Cetuximab has been investigated in combination with several different chemotherapy regimens. In the GORTEC study, the combination of docetaxel, cisplatin and cetuximab (TPEx) demonstrated promising efficacy, with ORR of 51.9%, PFS of 6.2 months and median OS of 14.0 months [8]. Chemotherapy consisted of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, every 3 weeks for up to 4 cycles. Cetuximab was given weekly until disease progression or unacceptable toxicities were observed. Because half of those patients who did not receive granulocyte colony-stimulating factor (G-CSF) support after each cycle developed grade 4 neutropenia, the revised protocol requested prophylactic G-CSF support, leading to a reduced incidence of grade 4 neutropenia and febrile neutropenia. In general, primary prophylaxis may be used to maintain dose-dense or dose-intense chemotherapy strategies that have survival benefits [9]. However, the survival benefits of dose-intensity or dose-density chemotherapy for patients with R/M SCCHN remains unclear. Moreover, this regimen required hospitalization for hydration.

Because the clinical outcome of patients with R/M cancer remains limited, quality of life during treatment is very important. Ideally, treatment extends survival while ensuring a good quality of life. We therefore planned to conduct a study of PCE, consisting of paclitaxel at a dose of 100 mg/m^2 on day 1 and day 8, and carboplatin AUC 2.5 on day 1 and day 8, repeated every 3 weeks for up to 6 cycles; and cetuximab given weekly until disease progression or unacceptable toxicities were observed.

Table 3. Adverse events[a] during PCE ($n = 47$)

Adverse events	Number of patients				
	Gr1	Gr2	Gr3	Gr4	%Gr3–4
Neutropenia	2	9	19	13	68
Rash acneiform	14	23	2	0	4
Skin reaction[b]	12	20	7	0	15
Febrile neutropenia	–	–	4	0	9
Anemia	21	22	3	0	6
Anorexia	13	9	3	0	6
Hyponatremia	16	0	2	0	4
Hypomagnesemia	24	3	1	1	4
Diarrhea	7	2	1	0	2
Nausea	10	3	1	0	2
Peripheral neuropathy	19	6	1	0	2
Mucositis	10	8	1	0	2
Hypoalbuminemia	30	6	1	0	2
Hypocalcemia	7	2	0	1	2
ALT increased	13	2	1	0	2
Alopecia	16	22	–	–	0
Constipation	17	6	0	0	0
Dysgeusia	8	5	0	0	0
Hypokalemia	10	1	0	0	0
Thrombocytopenia	28	1	0	0	0
AST increased	23	0	0	0	0
Hyperbilirubinemia	10	0	0	0	0

[a]Grade 1 or worse adverse events in 10% or more of patients.
[b]Excluded rash acneiform.

Several different regimens for paclitaxel plus carboplatin are commonly used [5, 10, 11]. To enable comparison with the PFE regimen in a planned phase III trial, we selected the 3-week regimen. The rationale for the dose and schedule of paclitaxel is as follows. In a previous phase II study of PCE, paclitaxel was administered at 200 mg/m^2, repeated every 3 weeks [5]. However, higher doses of paclitaxel are associated with an increased incidence of neuropathy, with the result that a weekly regimen is now widely used. Furthermore, our previous phase II study demonstrated that weekly administration of paclitaxel at 100 mg/m^2 showed promising activity with acceptable toxicities for patients with R/M SCCHN [12]. The rationale of the dose and schedule of carboplatin is as follows. The target AUC 5 of carboplatin is equivalent to a dose of cisplatin 100 mg/m^2, repeated every 3 weeks [13]. To maintain the dose intensity of paclitaxel, however, it is essential to avoid treatment interruption on day 8, leading to divided administration of carboplatin on day 1 and day 8. Based on this rationale, we selected a target AUC of 2.5 on days 1 and 8, repeated every 3 weeks.

PCE has several advantages. First, the chemotherapy dose can be adjusted weekly in accordance with adverse events, allowing the avoidance of severe adverse events and thereby ensuring a good quality of life. In fact, grade 3 or 4 neutropenia was observed in 68%, while only 9% of patients developed grade 3 febrile neutropenia. Moreover, the incidence of GI toxicities was markedly lower than that in previous studies of the EXTREME regimen [2, 14].

Although the comparison of phase II and III study data is risky, treatment compliance with the median cycle of chemotherapy (6 versus 5) was also better than that in the EXTREME study [2]. Moreover, the median duration of each drug was also comparable with that of the EXTREME study (carboplatin, 16.3 versus 18 weeks; cetuximab, 22 versus18 weeks).

Second, PCE allows treatment delivery in the outpatient clinic, which provides for more time to be spent with family. Moreover, 32 (68%) patients received second-line therapy and 14 (31%) received third-line therapy, indicating that most patients could receive subsequent therapy due to their maintenance of a good performance status by a less toxic first-line regimen.

Recently, immune checkpoint inhibitors such as anti-PD-1/PDL-1 antibody have demonstrated promising efficacy [15, 16]. Furthermore, nivolumab significantly improved overall survival over investigator's choice in patients with platinum-resistant R/M SCCHN [16]. In the present study, a total of nine patients (four second-line and five third-line) received immune checkpoint inhibitors, including anti-PD-1/PDL-1 antibody, in clinical trials. Although the survival benefit of these subsequent therapies in our present study remains unclear, a higher proportion of subsequent therapy may impact better survival, with a medial overall survival of 14.7 months.

Conclusion

In conclusion, the combination PCE used in this study showed promising efficacy with acceptable toxicity. Further evaluation of PCE in a phase III trial is warranted and we are currently planning a randomized trial of PCE versus PFE for first-line R/M SCCHN.

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Disclosure

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References

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999; 80(6): 827–841.
2. Vermorken JB, Mesia R, Rivera F et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008; 359(11): 1116–1127.
3. Gregoire V, Lefebvre JL, Licitra L et al. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21(Suppl 5): v184–v186.
4. Adelstein D, Gillison ML, Pfister DG et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 2.2017. J Natl Compr Canc Netw 2017; 15: 761–770.
5. Buentzel J, de Vries A, Micke O. Experience with cetuximab plus paclitaxel/carboplatinum in primary platinum-resistant recurrent head and neck cancer. In 2007 ASCO Annual Meeting. J Clin Oncol 2007; 18S (Suppl): 6077.
6. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228–247.
7. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53(282): 457–481.
8. Guigay J, Fayette J, Dillies AF et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. Ann Oncol 2015; 26(9): 1941–1947.
9. Smith TJ, Bohlke K, Lyman GH et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015; 33(28): 3199–3212.
10. Kies MS, Holsinger FC, Lee JJ et al. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. J Clin Oncol 2010; 28(1): 8–14.

11. Wanebo HJ, Lee J, Burtness BA et al. Induction cetuximab, paclitaxel, and carboplatin followed by chemoradiation with cetuximab, paclitaxel, and carboplatin for stage III/IV head and neck squamous cancer: a phase II ECOG-ACRIN trial (E2303). Ann Oncol 2014; 25: 2036–2041.
12. Tahara M, Minami H, Hasegawa Y et al. Weekly paclitaxel in patients with recurrent or metastatic head and neck cancer. Cancer Chemother Pharmacol 2011; 68(3): 769–776.
13. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 1999; 17: 409–422.
14. Yoshino T, Hasegawa Y, Takahashi S et al. Platinum-based chemotherapy plus cetuximab for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: results of a phase II trial. Jpn J Clin Oncol 2013; 43(5): 524–531.
15. Seiwert TY, Burtness B, Mehra R et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016; 17(7): 956–965.
16. Ferris RL, Blumenschein G, Jr., Fayette J et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016; 375(19): 1856–1867.