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Phase I trial of concurrent chemoradiotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF-CRT) for locally advanced squamous cell carcinoma of the external auditory canal

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Abstract

Porpose: Chemoradiotherapy with docetaxel (DOC), cisplatin (CDDP), and 5-FU (TPF-CRT) for locally advanced external auditory canal cancer (EACC) has favorable oncological and functional outcomes. To establish TPF-CRT as a standard of care for advanced EACC, we conducted this study to determine the maximum tolerated (MTD) and recommended dose (RD) of DOC in TPF-CRT for locally advanced EACC.

Methods: To determine the recommended (RD), and maximum tolerated dose (MTD) of DOC in TPF-CRT for EACC, a phase I trial was conducted using the standard "3+3" design for maximum dose finding. DOC was administered twice every four weeks, CDDP at 70 mg/m^2 and 5-FU at 700 mg/m^2; patients were also receiving radiotherapy (66 Gy). Eight patients with T3 or T4 EACC were prospectively enrolled.

Results: Two patients treated with DOC, 50 mg/m^2, and one out of six patients treated with DOC, 40 mg/m^2, had dose-limiting toxicities. Prolonged febrile neutropenia was observed in three patients. Grade 3 non-hematological toxicities were observed in only three patients. At study completion, six patients survived, five of whom were disease-free.

Conclusion: The RD and MTD of DOC in TPF-CRT for locally advanced EACC are 40 mg/m^2, when doses of CDDP and 5FU are 70 mg/m^2 and 700 mg/m^2, respectively.

(202 words)

Introduction

Squamous cell carcinoma of the external auditory canal (EACC) is an extremely rare entity with an annual incidence estimated between 1 and 6 cases per million.[1] While early EACC is successfully treated by sleeve resection or lateral temporal bone resection, surgical treatment for more advanced EACC requires subtotal temporal resection, resulting in facial palsy, hearing impairment and balance disorder with severe postoperative complications such as cerebral infarction and meningitis. The modified Pittsburgh classification, proposed by Moody et al.[2] in 2000, is most commonly used for EACC. According to this classification, oncological results for patients with T1, T2, and T3 are favorable, but survival rates of patients with T4 are extremely poor.[3-7]

At present, a standard treatment for locally advanced EACC has not been established. While most reports indicate that surgery is the first choice of treatment for advanced EACC, control rates are unfavorable, with serious surgical complications and postoperative dysfunction. Local control rates of advanced EACC, after treatment with CDDP-based single-agent concurrent chemoradiotherapy (CDDP-CRT), which has been established as the standard of care for locally advanced head and neck squamous cell carcinoma, are also unsatisfactory.[8]

To enhance the therapeutic effect of concurrent chemoradiotherapy, several trials of

concurrent multi-agent chemotherapy combined with radiotherapy, in advanced head and neck cancer, were conducted in the 1990s. However, multi-agent CRT was not established as the standard of care due to severe toxicities.[9] Recently, Shiga et al. reported successful oncological outcomes after CRT with docetaxel (DOC), cisplatin (CDDP), and 5-fluorouracil (5FU) (TPF-CRT) in advanced EACC[10, 11] with acceptable short-and long-term adverse events.[12] In addition, a multi-institutional retrospective study also reported satisfactory survival rates of patients with T3 and T4 EACC treated with TPF-CRT. The 5-year overall survival rates of patients with T3 and T4 EACC treated with TPF-CRT were significantly higher than those treated with CDDP-CRT (64.4% vs. 36.7%).[8] Currently, TPF-CRT is recognized as a promising treatment option for advanced EACC. However, the doses of agents used in TPF-CRT vary depending on the institution, and optimal doses have not yet been determined.

To establish TPF-CRT as a standard of care for advanced EACC, we conducted this study to determine the maximum tolerated (MTD) and recommended dose (RD) of DOC in TPF-CRT for locally advanced EACC.

Methods

Study Design

This was a phase I trial of docetaxel in combination with cisplatin and 5-FU in TPF-CRT using a standard “3+3” dose escalation design. All procedures were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. The trial was approved by the Institutional Review Board of the University of Kobe (#1385). All patients gave a written informed consent.

Eligibility Criteria

Eligibility criteria were as follows: 1) newly diagnosed, previously untreated, histologically confirmed squamous cell carcinoma arising from the external or middle auditory canal; 2) T3 or T4 disease and any N stage according to the modified Pittsburgh classification; 3) no distant metastatic disease; 4) age ranging from 20 to 75 years; 5) Eastern Cooperative Oncology Group(ECOG) performance status of 0 or 1, 6) no previous history of radiotherapy in the head and neck lesion, 7) no chemotherapy for other carcinomas within three years, 8) retention of major organ function and laboratory test values meeting the following criteria at least within 14 days before enrollment: white blood cell $\geq$ 3000/mm^3, neutrophils $\geq$ 1500/㎜^{3}, platelet $\geq$ 10 $\times$ 104/mm^3, hemoglobin $\geq$ 9.0 g/dL, total-bilirubin $\leq$ 1.5 mg/dL, creatinine $\leq$ 1.2 mg/dL or creatinine clearance $\geq$ 60ml/min.

Exclusion Criteria

Exclusion criteria were as follows: 1) severe uncontrolled intercurrent illness including

symptomatic congestive heart failure, unstable angina pectoris, unstable cardiac arrhythmia, uncontrollable hypertension, or any other condition or circumstance that could interfere with adherence to the study's procedures; 2) prior treatment with any of the chemotherapy medications; 3) prior bone marrow transplant or history of organ transplant requiring the need for any chronic immunosuppressive medications; 4) major psychiatric disorders that would limit compliance; 5) active infection requiring systemic antibiotic therapy; 6) pregnant or breast-feeding females; 7) known prior severe allergy or hypersensitivity to the chemotherapy or any of the components of the study treatment.

Protocol Treatment

The treatment plan is shown in Figure 1. Sixty-six Gy of radiotherapy were administered in total (five times per week, 2 Gy per fraction). On day 1, DOC, 70 mg/m^2 of CDDP, and 700 mg/m^2 of 5-FU were infused. Chemotherapy was administered on day 29. The starting dose of DOC was 50 mg/m^2 (dose level 1). The “3 + 3” method was used for dose determination. If no dose-limiting toxicities (DLTs) were observed in three patients, the dose was escalated to the next level (60 mg/m^2). If DLTs were observed in one of three patients, three more patients were enrolled at that level. If DLTs were observed in two or more of three patients, the dose level was de-escalated (40 mg/m^2). We treated at least six patients with the same dose; the dose was defined as RD if DLTs were observed in two or less; MTD was defined as

the highest dose that DLT frequency was lower to 33%. The MTD and RD were determined by considering the observed toxicity and tolerability.

Toxicity Assessment

Toxicity was assessed once per cycle according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0. DLT was defined as grade 4 or higher neutrophil depletion lasting eight days or longer, febrile neutropenia lasting four days or longer, grade 4 thrombocytopenia, grade 3 or higher non-hematological toxicity (excluding grade 3 anorexia, nausea, vomiting, oral and pharyngeal mucositis, dermatitis, and electrolyte abnormalities), discontinuation of protocol treatment due to adverse events, even when the physician determined that dose reduction was necessary to ensure patient safety.

Radiation Therapy Suspension Criteria

Radiation therapy was suspended for one day, if the patient met the following criteria: febrile neutropenia, grade 4 oral or pharyngeal mucositis, use of G-CSF, or patient refusal of radiotherapy. If radiation therapy ceased for 14 days, treatment was discontinued.

Second Chemotherapy Dose Reduction Criteria

DOC dose decreased by one level if DLTs were observed during the first course of chemotherapy. CDDP and 5-FU doses were reduced to 80% of the dose if the patients met the following criteria: white blood cell count < 1000/mm^3, neutrophils < 500/㎜ ^{3}, platelet

count < 2.5 × x $10^4/mm^3$, and febrile neutropenia. CDDP dose was reduced to 80% % of the dose if creatinine clearance was < 60 ml/min.

Evaluation of Oncological Outcomes

Oncological outcomes were assessed by magnetic resonance imaging (MRI) of the primary sites. Treatment effects were estimated based on changes in tumor size. Complete response (CR) was defined as complete disappearance of all measurable lesions three months after the end of the treatment. A partial response (PR) was defined as ≥ 70% reduction of the the greatest diameters in measurable lesions. Stable disease (SD) was defined as less than 70% reduction in diameter. Progressive disease (PD) was indicated by ≥ 20% increase in tumor diameter or the appearance of new lesions.

Results

From 2014 to 2019, eight patients were enrolled in this study. The characteristics of the patients are shown in Table1. Five patients were male, and three were female. Age ranged from 51 to 70 years, with a mean of 60 years. ECOG performance status was 0 in all patients. One patient had a T3 tumor and seven patients had T4 tumors. No patient had lymph node or distant metastasis. Among the seven T4 tumors, four were considered inoperable due to extensive dura invasion or apparent involvement of the brain, internal

carotid artery, or internal jugular vein. The observation period ranged from 12 to 75 months (mean 34.1 months, median 33 months). No 3, 6, and 8 patients were found to have facial paralysis . Hearing test was not performed.

All patients completed the protocol treatment. For the first two patients treated with dose level 1, DLTs (febrile neutropenia) lasted six and eight days, respectively. Thus, the next three patients were treated with a dose level of 0 (DOC: 40 mg/m^2). Only one out of three patients had DLTs (febrile neutropenia) lasting four days, but no DLTs were observed in the other two patients. Accordingly, the next three patients were also treated with dose level 0. None of these three patients had any DLTs. In total, one out of six patients treated with dose level 0 had DLTs. As a result, dose level 0 was defined as RD and MTD.

The adverse events observed in all treatment courses are listed in Table 2. Grade 4 leukopenia and grade 4 neutropenia were observed in three patients and two patients, respectively. Febrile neutropenia occurred in three patients who had DLTs. Grade 3 non-hematological toxicities were observed in three patients: nausea in one patient, oral mucositis in one patient, and oral mucositis and dermatitis in one patient.

Oncological outcomes are presented in Table 3. The response rates observed at three months after the end of the treatment was CR in three patients and PR in five patients. Local recurrence was observed in four patients (median: 8 months). Two patients

underwent subtotal temporal bone resection. One patient died of local recurrence, and one patient was alive with a recurrent tumor. At the end of the study, five patients were disease-free, one patient had local recurrence, one patient had died of EACC, and one of pancreatic cancer. While no recurrence was observed in the two patients treated with DOC dose level 1, four out of six patients treated with dose level 0 had local recurrences.

Late adverse events that occurred during the observation period included osteonecrosis at the treatment site in one patient. Three patients who had facial nerve palsy before treatment showed no improvement after treatment. Hearing tests were not performed before treatment, making it difficult to compare the results before and after treatment. 4 patients had persistent otorrhea after treatment. There were no other late adverse events of note.

Discussion

CDDP-CRT has been widely used as the standard of care for the treatment of advanced head and neck squamous cell carcinoma. In the 1990s, to enhance the therapeutic effect of CRT, several trials of TPF-CRT for advanced head and neck cancer were conducted. However, TPF-CRT was not established as a standard of care due to high rates of severe toxicities. According to a report by Katori et al., grade 3 or higher mucositis was observed in 79% of the patients treated with TPF-CRT,[13] but not in patients with EACC.[10] The most probable reason for this disparity is the differences in the irradiation fields. Since the oral

cavity and pharynx are not irradiated in EACC treatment, adverse events such as mucositis are less likely to occur. Thus, patients with EACC can tolerate CRT-TPF without severe adverse events. To date, there are several reports on CRT-TPF in EACC, but the doses of the agents have not been determined, and their safety has not been proven. A multi-center study reported the superiority of CRT-TPF over CDDP-CRT but also showed that applied drug doses were not constistent.[8] Considering this background, this study was designed to evaluate the RD and MTD of DOC and safety of TPF-CRT for the treatment of advanced EACC. Once a phase I study is conducted and optimal doses are determined, it is necessary to verify whether this treatment can be safely administered as standard of care in advanced EACC.

Since EACC is quite rare, it is challenging to recruit a large number of participants. Therefore, we applied a standard phase I "3+3" dose escalation design to determine the optimal volume of DOC based on FP-CRT (CDDP: 70 mg/m^2 + 5-FU: 700 mg/m^2), which has been established for the treatment of nasopharyngeal cancers.[14] Due to the rarity of the disease, it took five years to complete the study. Since four out of eight patients had unresectable highly advanced disease, we believe that this study included particularly advanced T4 cases. DLTs were observed in three patients; all were febrile neutropenia lasting 4 days or longer, successfully managed with antibiotics and G-CSF, as in the case of

induction chemotherapy using TPF. Grade 3 non-hematological toxicities were observed in only three patients (nausea in one patient, oral mucositis in one patient, and oral mucositis and dermatitis in one patient). As expected, the incidence of mucositis was lower than previous reports of TPF-CRT for head and neck cancers. In the present study, the RD and MTD of DOC in TPF-CRT for EACC were defined at 40 mg/m^2.

At the end of study treatment, five out of eight patients were disease-free, and one patient was alive with disease. Although the number of cases was small, the survival rate was high for advanced EACC. Of note, local recurrence was observed in four out of six patients treated with dose level 0, while no local recurrence was observed in the two patients treated with dose level 1, suggesting that a reduction in DOC dose may increase the recurrence rate. Since febrile neutropenia can be managed with antibiotics and G-CSF, as shown in the present study, the MTD might be considered in patients with normal organ function.

This study has several limitations. Due to the rarity of the disease, it took a long time to complete this study. Use of antiemetics in later-enrolled patients was strengthened, in line with changes in the guidelines for antiemetic use. However, since none of the eight patients had grade 3 or higher nausea and/or vomiting, we believe that changes in antiemetics had little impact on the RD and MTD. Due to the small number of patients, we changed only the dose of DOC. Accordingly, our results showed that CDDP at 70 mg/m^2, 5-FU at 700

mg/m^2, and DOC at 40 mg/m^2 was the RD, but DOC volume was much lower than that of CDDP and 5-FU, resulting in an unbalanced dosage. To balance the volume of each drug, we may consider reducing the dose of CDDP and 5-FU to 60 mg/m^2 and 600 mg/m^2, respectively, and increasing the dose of DOC to 50 mg/m^2. Further verification is needed to confirm the safety of this treatment at a balanced dosage.

Conclusion

In this study, we investigated the RD and MTD of DOC and the safety of TPF-CRT for the treatment of advanced EACC. The RD and MTD of DOC in TPF-CRT for locally advanced EACC are 40 mg/m^2, when doses of CDDP and 5FU are 70 mg/m^2 and 700 mg/m^2, respectively.

Figure and Table

Figure 1 Treatment plan of this study

Sixty-six Gy of radiotherapy were administered in total (5 times per week, 2 Gy per fraction). On day 1, DOC, 70 mg/m^2 of CDDP, and 700 mg/m^2 of 5-FU were infused. Chemotherapy was administered on day 29.

Table 1 Patients' characteristics

Characteristics of eight enrolled patients.

Abbreviations: DLT, dose-limited toxicity; FN, facial nerve; ICA, internal carotid artery; IJV, internal jugular vein; F, female; L, left; M, male; P, parotid; R, right; TMJ, temporomandibular joint.

Table 2 Adverse event (CTCAE v4.0)

Grade 4 leukopenia and grade 4 neutropenia were observed in three patients and two patients, respectively. Febrile neutropenia occurred in three patients who had DLT. Grade 3 non-hematological toxicities were observed in three patients: nausea in one patient, oral mucositis in one patient, and oral mucositis and dermatitis in one patient.

Table 3 Outcomes

Oncological outcomes of eight patients.

The response rate was CR in three patients and PR in five patients. Local recurrence was observed in four patients. Two patients underwent salvage surgery. One patient died of local recurrence, and one survived with a recurrent tumor. At the end of the study, five patients were disease-free, one patient had a local recurrence, one patient had died of this disease, and one of pancreatic cancer.

Abbreviations: AWD, alive with disease; CR, complete response; DLT, dose-limited toxicity; DAD, dead with another disease; DOD, dead of this disease; NED, no evidence of disease; PR, partial response; RT, radiotherapy; STBR, subtotal temporal bone resection.

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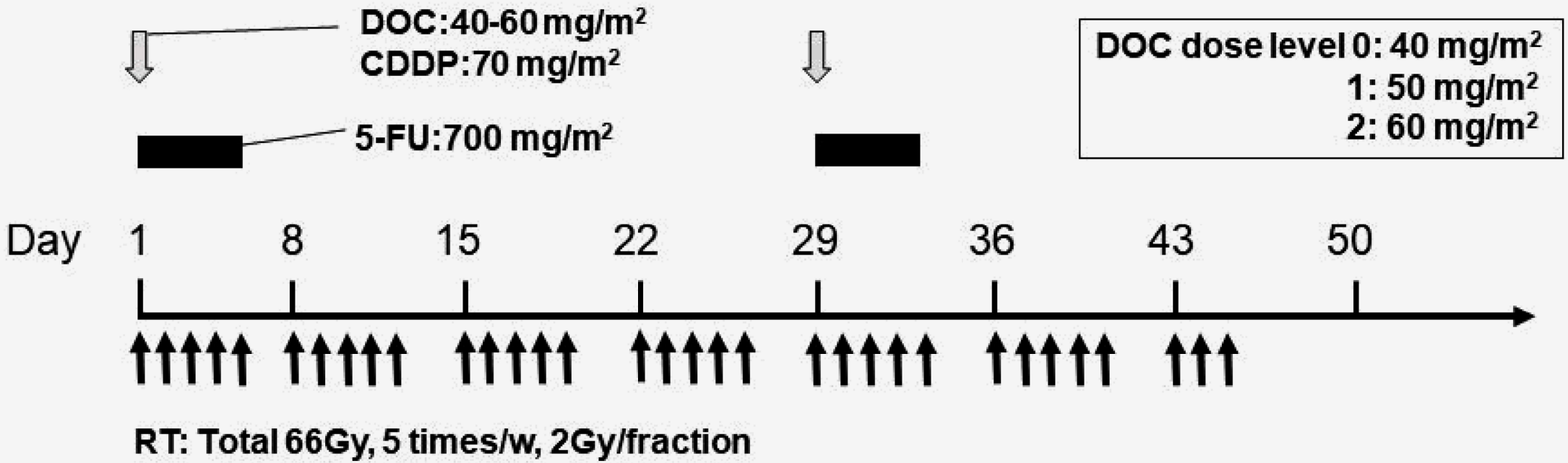
DOC:40-60 mg/m²
CDDP:70 mg/m²
5-FU:700 mg/m²
DOC dose level 0: 40 mg/m²
1: 50 mg/m²
2: 60 mg/m²
Day
1
8
15
22
29
36
43
50
RT: Total 66Gy, 5 times/w, 2Gy/fraction

Table 1 Patients characteristics

Patient No.	Dose level	Sex	Age	T stage	N stage	Side	Operability	Invasion site	DLT
1	1	M	67	4	0	R	Inoperable	IJV, P, TMJ, skin	+
2	1	M	54	3	0	L	Operable	-	+
—									
3	0	F	59	4	0	R	Inoperable	Dura, FN	+
4	0	F	70	4	0	L	Operable	TMJ, skin, P	-
5	0	F	64	4	0	L	Operable	TMJ, P	-
6	0	M	51	4	0	L	Operable	FN, TMJ, skin, P	-
7	0	M	61	4	0	L	Inoperable	Dura, Brain, IJV,	-
8	0	M	54	4	0	L	Inoperable	Dura, ICA, FN, PA, TMJ	-

Characteristics of eight enrolled patients.

Abbreviations: DLT, dose-limited toxicity; FN, facial nerve; ICA, internal carotid artery; IJV, internal jugular vein; F, female; L, left; M, male; P, parotid; R, right; TMJ, temporomandibular joint.

Table 2 Adverse event (CTCAE v4.0)

Term	Grade 1	Grade2	Grade3	Grade4
Constipation	1			
Diarrhea	4			
Dry mouth	7			
Nausea	3	3	1	
Oral mucositis	3	2	2	
Vomiting	1	1		
Radiation dermatitis	5	2	1	
Acneform rush	1			
Fatigue	3	4		
Fever	3			
Febrile Neutropenia			3	
Dysgeusia	4	2		
Anxiety	1			
Depression	1			
Delirium	1			
Alopecia	4	3		
Hiccups	2	1		
Weight loss	5	2		
AST/ALT increase	1	1		
Hyponatremia	3			
Creatinine increased	1			
Hypoalbuminemia	4			
WBC decreased	1		1	3
Neutrophile count decrease	1		2	2
Platelet count decrease	2	1		
Hemoglobin decreased	3	1		

Grade 4 leukopenia and grade 4 neutropenia were observed in three patients and two patients, respectively. Febrile neutropenia occurred in three patients who had DLT. Grade 3 non-hematological toxicities were observed in three patients: nausea in one patient, oral mucositis in one patient, and oral mucositis and dermatitis in one patient.

Table 3 Outcome

Patient No.	Dose level	DLT	RT delay	Dose reduction	Response	Local recurrence	Pre-treatment operability	Salvage operation	Survival	Observation period
1	1	+	6 days	+	CR	No	Inoperable	-	DAD	18M
2	1	+	10 days	+	PR	No	Operable	-	NED	75M
3	0	+	4 days	+	CR	No	Inoperable	-	NED	52M
4	0	-	-	+	PR	Yes (8M)	Operable	STBR	NED	43M
5	0	-	-	+	PR	No	Operable	-	NED	42M
6	0	-	-	-	PR	Yes (8M)	Operable	STBR	NED	24M
7	0	-	-	-	CR	Yes (14M)	Inoperable	Inoperable	AWD	23M
8	0	-	-	-	PR	Yes (6M)	Inoperable	Inoperable	DOD	12M

Oncological outcomes of eight patients.

The response rate was CR in three patients and PR in five patients. Local recurrence was observed in four patients. Two patients underwent salvage surgery. One patient died of local recurrence, and one survived with a recurrent tumor. At the end of the study, five patients were disease-free, one patient had a local recurrence, one patient had died of this disease, and one of pancreatic cancer.

Abbreviations: AWD, alive with disease; CR, complete response; DLT, dose-limited toxicity; DAD, dead with another disease; DOD, dead of this disease; NED, no evidence of disease; PR, partial response; RT, radiotherapy; STBR, subtotal temporal bone resection.