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Induction Chemotherapy With 5-Fluorouracil, Cisplatin, and Cetuximab in Advanced Head and Neck Squamous Cell Carcinoma

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Abstract. *Background/Aim: Chemoradiotherapy (CRT) with high-dose cisplatin has become the standard of care for larynx preservation in patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). However, the long-term results are unsatisfactory. Induction chemotherapy (ICT) with docetaxel/cisplatin/5-fluorouracil (TPF) is associated with hematologic toxicity, and a safer therapy with comparable efficacy is desired. We conducted a pilot study to investigate the efficacy and safety of 5-fluorouracil/cisplatin/cetuximab (FPE) therapy as a candidate regimen for ICT in comparison with TPF. Patients and Methods: Patients with stage cN2/3 LA-SCCHN of the larynx/oropharynx/hypopharynx were treated with FPE or TPF followed by radiotherapy. We reviewed patients' medical records and evaluated treatment efficacy and safety retrospectively. Results: The response rates for ICT and ICT–radiotherapy were 71% and 93%, respectively, in the FPE group and 90% and 89%, respectively, in the TPF group. The 1-year progression-free and overall survival rates were 57% and 100%, respectively, in the FPE group and 70% and 90%, respectively, in the TPF group. TPF was linked to significantly higher rates of Grade 3/4 hematologic toxicity during ICT. The rates of Grade 3 or higher toxicity did not differ between the two groups during radiotherapy. Conclusion: The efficacy of ICT was comparable between the FPE and TPF groups, whereas FPE was associated with less toxicity. It is suggested that FPE therapy is an alternative ICT regimen to TPF therapy, but further long-term follow-up is needed.*

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Chemoradiotherapy (CRT) with high-dose cisplatin became the standard of care for larynx preservation in the treatment of locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) after the RTOG91-11 study found that the rates of laryngeal preservation and locoregional control were higher for CRT than for induction chemotherapy (ICT) followed by radiotherapy (RT) or RT alone (1). However, the long-term results of the same trial illustrated that although the laryngeal preservation and locoregional control rates remained superior in the CRT group, the larynx preservation rate was better in the ICT–RT group than in the CRT group, and the overall survival (OS) rate was the lowest in the CRT group (2). This was attributable to an unexplained increase in deaths unrelated to cancer in the CRT group, and the authors concluded that new strategies focusing on improved locoregional control should be developed. Although the details of late complications were not given, it can be assumed that aspiration pneumonia or malnutrition can occur because of decreased swallowing function. It is necessary to develop treatment strategies that both preserve the larynx as an organ and minimise the impact on swallowing function. However, docetaxel/cisplatin/5-fluorouracil (5-FU) combination therapy (TPF), which is currently the standard therapy for ICT, is often associated with hematologic toxicities such as febrile neutropenia, and a safer therapy with comparable efficacy is desired. We conducted a pilot study to investigate the efficacy and safety of 5-FU/cisplatin/cetuximab (FPE) therapy as a candidate for ICT with similar efficacy and greater safety than TPF therapy.

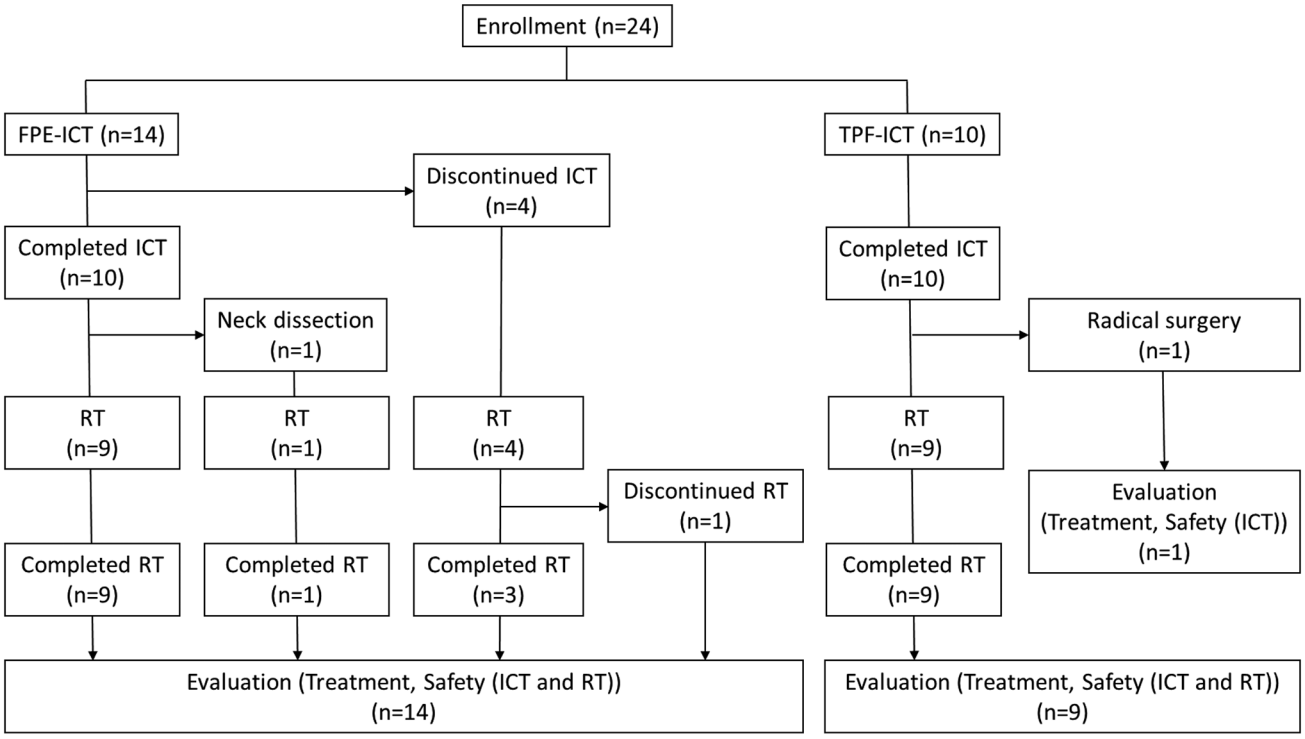

Figure 1. *Summary of the treatment course. ICT: Induction chemotherapy; FPE: 5-fluorouracil/cisplatin/cetuximab; TPF: docetaxel/cisplatin/5-fluorouracil; RT: radiation therapy.*

Patients and Methods

Patients. Patients with operable stage cN2/3 LA-SCCHN of the larynx/oropharynx/hypopharynx (according to the American Joint Committee on Cancer/Union for International Cancer Control classification 8th edition) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 who were treated at our institution between February 2018 and January 2021 were eligible for this study. Patients who did not wish to participate in the study or similar patients who were considered eligible for ICT for cN1 stage disease during the same period were treated with TPF, and these patients comprised the control group. This study was approved by the Institutional Review Board of Saga University (Approval No. 2017-11-05).

Treatment. FPE was administered using the EXTREME study regimen (3). The doses of cisplatin and 5-FU for FPE were reduced by 20% from the original regimen to 80 and 800 mg/m^2, respectively. The doses of cisplatin and 5-FU for TPF were also reduced from the original doses in the TAX324 study (4). The doses of docetaxel, cisplatin, and 5-FU were 60, 70, and 750 mg/m^2, respectively. Patients completed up to three cycles of ICT, and when a complete response (CR) or partial response (PR) was obtained, patients underwent RT. Subsequent RT was based on the Bonner regimen with cetuximab (5). Patients with stable disease (SD) or progressive disease (PD) underwent radical surgery, but those who refused radical surgery received RT. Patients who could not receive cetuximab because of adverse events after treatment initiation were treated with CRT consisting of low-dose cisplatin (weekly 25 mg/m^2, seven cycles) plus S-1 (60 mg/m^2, days 1-14 and 29-42).

Treatment evaluation. We reviewed the medical records of patients and evaluated the efficacy and safety of FPE and TPF followed by RT retrospectively. The primary endpoint was the response rate, and secondary endpoints were safety, progression-free survival (PFS), and compliance. Treatment response was evaluated in all patients who started treatment (intention-to-treat analysis) according to Response Evaluation Criteria in Solid Tumors version 1.1. Safety was evaluated according to the Common Terminology Criteria for Adverse Events v4.0. The safety evaluation of ICT was performed in all patients, and that of RT was performed in all patients excluding one who underwent radical surgery without RT (Figure 1). The completion of RT was defined as completion of the scheduled 70-Gy dose in the 23 patients who started RT.

Statistical analysis. Fisher's exact test was used to compare response rates and adverse events between the TPF and FPE groups, and the log-rank test was used for 1-year PFS and OS. All statistical analyses were performed using JMP Pro 17.0.0 (JMP Statistical Discovery LLC, Cary, NC, USA). All tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

Patient background (Table I). Fourteen patients were enrolled in the FPE ICT study. Ten patients who received TPF served

Table I. *Patient characteristics*.

	FPE (N=14)	TPF (N=10)
Male - cases (%)	10 (71)	10 (100)
ECOG PS 0 - cases (%)	14 (100)	10 (100)
Age - years		
Median	62	66
Range	51-72	54-78
Primary site - cases (%)		
Oropharynx p16-positive	4 (29)	4 (40)
Oropharynx p16-negative	1 (7.1)	1 (10)
Hypopharynx	6 (43)	5 (50)
Larynx	3 (21)	0
T classification - cases (%)		
T1	1 (7.1)	0
T2	5 (36)	3 (30)
T3	4 (29)	4 (40)
T4	3 (21)	2 (20)
T4a	1 (7.1)	0
T4b	0	1 (10)
N classification - cases (%)		
N1	0	3 (30)
N2	4 (29)	2 (20)
N2b	5 (36)	1 (10)
N2c	1 (7.1)	0
N3b	4 (29)	4 (40)
Stage - cases (%)		
II	0	2 (20)
III	4 (29)	3 (30)
IV A	6 (43)	0
IV B	4 (29)	5 (50)

FPE: 5-FU/cisplatin/cetuximab; TPF: docetaxel/cisplatin/5-FU; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

as the control group. Median age was higher in the TPF group (66 years; range=54-78 years) than that in the FPE group (62 years; range=51-72 years). All patients had ECOG PS 0. In the TPF group, three patients had N1 stage disease, including two patients with a p16-positive lesion in the oropharynx and one patient with a lesion in the hypopharynx. Four patients had N3b stage disease in each group.

Treatment course (Table II, Figure 1). In the FPE group, four patients discontinued treatment because of adverse events in the first cycle of ICT. The adverse events were grade 4 (G4) alanine aminotransferase (AST)/aspartate aminotransferase (ALT) elevation, G3 infusion-related reaction, G2 prolonged leukopenia, and G1 pneumonitis in one patient each. The remaining patients completed three cycles of ICT. In one patient, the cisplatin dose was reduced in the second cycle because of renal dysfunction. One patient who completed ICT underwent neck dissection before RT, and the primary tumour was treated by subsequent RT with cetuximab (BRT). The completion rates of ICT and RT were 71% and 93%, respectively.

Table II. *Treatment course*.

	FPE (N=14)	TPF (N=10)
Treatment completion - cases (%)		
ICT	10 (71)	10 (100)
RT	13 (93)	9 (100)
ICT cycles - cases (%)		
1	4 (29)	0
2	0	8 (80)
3	10 (71)	2 (20)
ICT dose reduction - cases (%)		
Yes	5 (36)	10 (100)
No	9 (64)	0
RT concomitant drugs - cases (%)		
Cetuximab	12 (86)	10 (100)
Cisplatin/S-1	2 (14)	0

FPE: 5-FU/cisplatin/cetuximab; TPF: docetaxel/cisplatin/5-FU; ICT: induction chemotherapy; RT: radiotherapy.

In the TPF group, ICT was completed in all 10 patients, but the dose of chemotherapy after the second cycle was reduced in all patients. Seven patients required a reduction of the docetaxel dose because of hematologic toxicity, one patient required cisplatin dose reduction because of renal dysfunction, and two patients required docetaxel and cisplatin dose reduction because of hematologic toxicity and renal dysfunction. Two patients received prophylactic pegfilgrastim in the second cycle. The ICT and RT completion rates were both 100%.

Treatment outcomes (Table III). The response rates were 71% and 90% in the FPE (three CRs and seven PRs) and TPF groups (two CRs and seven PRs), respectively (p=0.3577). The response rates for ICT–RT were 93% and 89% in the FPE (10 CRs and 3 PRs) and TPF groups (seven CR and one PR), respectively (p=0.5504). For the one patient in whom PR was obtained with ICT but neck dissection was performed before BRT, the response to ICT–RT was judged as PR because CR was obtained with BRT for the primary tumour after neck dissection. The 1-year PFS rates were 57% in the FPE group and 70% in the TPF group (p=0.9154). The 1-year OS rates in these groups were 100% and 90%, respectively (p=0.4375).

Safety. G3 or higher adverse events during ICT are listed in Table IV. No G4/5 adverse events were observed in the FPE group. The G3 adverse events were neutropenia in three patients (21%), anorexia in two patients (14%), hepatic dysfunction [increased ALT/AST/gamma-glutamyl transferase (GGT)], and infusion-related reaction in one patient (7.1%). Cetuximab-related adverse events included G3 infusion-related reaction in one patient (7.1%), G1

Table III. *Treatment efficacy.*

	FPE (N=14)	TPF (N=10)	*p*-Value
PFS - %			
1-year	57	70	0.9154
OS - %			
1-year	100	90	0.4375
ICT response - cases (%)			
CR	3 (21)	2 (20)	
PR	7 (50)	7 (70)	
SD	3 (21)	1 (10)	
PD	1 (7.1)	0	
Response rate	10 (71)	9 (90)	0.3577
ICT-RT response - cases (%)			
CR	10 (71)	7 (78)	
PR	3 (21)	1 (11)	
SD	1 (7.1)	1 (11)	
PD	0	0	
Response rate	13 (93)	8 (89)	0.5504

FPE: 5-FU/cisplatin/cetuximab; TPF: docetaxel/cisplatin/5-FU; RT: radiotherapy; ICT: induction chemotherapy; PFS: progression-free survival; OS: overall survival; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table IV. *Induction therapy adverse events (Grade 3-4).*

	FPE (N=14)	TPF (N=10)	*p*-Value
	Cases (%)		
Leukopenia	0	6 (60)	0.0016
Neutropenia	3 (21)	9 (90)	0.0028
Febrile neutropenia	0	4 (40)	0.0198
Mucositis	0	1 (10)	0.4167
Anorexia	2 (14)	3 (30)	0.6146
Hypokalemia	0	1 (10)	0.4167
Hyperkalemia	0	1 (10)	0.4167
ALT increased	1 (7.1)	0	1.0000
AST increased	1 (7.1)	0	1.0000
GGT increased	1 (7.1)	2 (20)	0.5504
Hypoalbuminemia	0	1 (10)	0.4167
Infusion related reaction	1 (7.1)	0	1.0000

FPE: 5-FU/cisplatin/cetuximab; TPF: docetaxel/cisplatin/5-FU; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase.

infusion-related in two patients (14%), G1 pneumonitis in one patient (7.1%), G1/2 acne-like skin rash in seven patients (50%), and G1/2 paronychia in two patients (14%). G3 or higher adverse events in the TPF group included neutropenia in nine patients (90%; G4 in seven patients and G3 in two patients), leukopenia in six patients (60%; G4 in one patient and G3 in five patients), G3 febrile neutropenia in four patients (40%), G3 anorexia in three patients (30%), and G3 GGT elevation in two patients (20%). The TPF group exhibited significantly higher rates of hematologic toxicity (leukopenia, p=0.0016; neutropenia, p=0.0028; and febrile neutropenia, p=0.0198).

G3 or higher adverse events during RT are listed in Table V. No G4/5 adverse events were observed in the FPE group, and G3 adverse events included mucositis and radiation dermatitis in six patients (43%) each, anorexia in five patients (36%), and acne-like rash in three patients (21%). In the TPF group, G4 or higher adverse events included one case each of G4 leukopenia/neutropenia and G5 dehydration. G3 adverse events included anorexia in five patients (56%), mucositis in three patients (33%), and radiation dermatitis in two patients (22%). The rates of hematologic toxicity did not differ between the groups.

Discussion

CRT with high-dose cisplatin has been established as the standard of care for larynx preservation in the treatment of locally advanced laryngeal and pharyngeal cancer. At the same time, managing adverse events such as dysphagia and renal dysfunction is an important issue. The long-term results of the RTOG91-11 trial, which compared CRT with high-dose cisplatin (CRT group), ICT with cisplatin/5-FU followed by RT alone (ICT–RT group), and RT alone (RT group)(2), revealed that the ICT–RT group had the best laryngectomy-free survival and OS rates, indicating that ICT is useful when the preservation of laryngeal function and impact of treatment on the patient's general condition are considered. Based on the principle that survival is the most important goal in the treatment of LA-SCCHN and that laryngeal preservation should be attempted, if possible, ICT–RT is considered a better treatment than CRT over a 10-year period. However, it was not demonstrated whether the combination of ICT with FPE followed by BRT, as in our study, causes fewer late complications than high-dose cisplatin-based CRT. Although further investigation is needed to determine the actual severity of post-treatment dysphagia and long-term prognosis, ICT with FPE could be an alternative treatment to preserve laryngeal function.

The benefit of TPF was reported in the TAX324 study, and it is currently the standard treatment for ICT (6). The study recorded significantly longer OS and a better locoregional control rate for TPF than for cisplatin/5-FU. The incidence of distant metastasis was lower with TPF, although the difference was not significant. Conversely, the PARADIGM study directly compared ICT with TPF followed by CRT and cisplatin-based CRT. The study, which ended without reaching the expected enrolment, revealed no difference between the two groups (7). However, excluding patients

Table V. *Radiotherapy adverse events (G3-5).*

	Cases (%)		
Leukopenia	1 (7.1)	1 (11)	1.0000
Neutropenia	0	1 (11)	0.3913
Febrile neutropenia	0	1 (11)	0.3913
Mucositis	6 (43)	3 (33)	1.0000
Radiation dermatitis	6 (43)	2 (22)	0.3998
Acne-like skin rash	3 (21)	0	0.2530
Anorexia	5 (36)	5 (56)	0.4173
Nausea	1 (7.1)	1 (11)	1.0000
Fatigue	0	1 (11)	0.3913
Dehydration	0	1* (11)	0.3913
Insomnia	1 (7.1)	0	1.0000
Dysgeusia	1 (7.1)	0	1.0000
Hearing impaired	1 (7.1)	0	1.0000
Catheter related infection	1 (7.1)	0	1.0000
Arterial thromboembolism	1 (7.1)	0	1.0000
Urinary tract infection	1 (7.1)	0	1.0000
Lung infection	0	2 (22)	0.1423

FPE: 5-FU/cisplatin/cetuximab; TPF: docetaxel/cisplatin/5-FU. *Grade 5 case.

with oropharyngeal lesions, the 3-year PFS rate tended to be better in the TPF+CRT group, and the incidence of distant metastasis tended to be lower in the TPF+CRT group. In the TTCC2503 trial reported in 2014, there were no significant differences in PFS and OS between these groups (8). Although the results of the long-term outcome study of the same trial were similar (9), the TPF+CRT group tended to have better PFS than the CRT group for laryngeal and hypopharyngeal cancers excluding oral cavity and oropharyngeal cancers, suggesting that TPF+RT is useful for laryngeal and hypopharyngeal cancers when considered together with the results of the PARADIGM trial. However, TPF therapy is often associated with hematologic toxicities such as febrile neutropenia, and there is a need for a safer treatment with comparable efficacy.

The purpose of this study was to evaluate the efficacy and safety of the EXTREME regimen (FPE), which is routinely used as the standard therapy for recurrent or metastatic head and neck cancer (10), as an alternative ICT regimen to TPF. Furthermore, this regimen has already been established as a treatment for metastatic disease, and it is expected to reduce the incidence of distant metastasis. In this study, patients with N2 or higher stage cancer were included because distant metastasis can occur in patients with advanced N stage cancer. We compared the FPE and TPF groups to evaluate the efficacy and safety of FPE followed by RT. The response, 1-year PFS, and 1-year OS rates were similar in the groups. Excluding the four patients in the FPE group who discontinued treatment after one cycle because of adverse events, the response rate was 100%, which could be interpreted as a good response to FPE if treatment was completed. Among the four patients who discontinued treatment in the FPE group, one case of prolonged leukopenia and one case of G4 liver dysfunction could have occurred with TPF therapy, but one case of infusion-related reaction and one case of interstitial pneumonia were considered to be cetuximab-related, which is one of the problems of FPE therapy. Regarding the safety of ICT, the frequency of hematologic toxicities such as leukopenia, neutropenia, and febrile neutropenia was significantly higher in the TPF group. In the FPE group, the only greater than G3 hematologic toxicity was neutropenia in 21% of patients, which could be treated safely. However, some adverse events such as infusion-related reactions and interstitial pneumonia could affect the subsequent treatment strategy. Interstitial pneumonia is considered an important problem because it limits the use of immune checkpoint inhibitors or cetuximab (11, 12) in the case of recurrence or metastasis. Regarding safety during RT after ICT, although there were no significant differences between the groups, hematologic toxicity and anorexia were more common in the TPF group. In the FPE group, mucositis, radiation dermatitis, and acne-like dermatitis, which appeared to be cetuximab-related, were more common because of the longer duration of cetuximab use. However, all of them were G3 or lower, and they were considered relatively safe to treat.

The limitations of this study included its single-centre, non-randomised, and retrospective nature, the small number of patients, and both FPE and TPF were given at reduced doses from the original regimens.

The efficacy and safety of ICT with FPE for larynx preservation in the treatment of locally advanced laryngeal, oropharyngeal, and hypopharyngeal cancer were investigated. The efficacy of ICT was comparable between the FPE and TPF groups. Regarding safety, FPE therapy could be administered safely compared with TPF therapy, but there were some cetuximab-related adverse events such as infusion-related reactions or interstitial pneumonia. It was suggested that FPE therapy could be an alternative ICT regimen to TPF therapy, but further long-term follow-up is needed.

Conflicts of Interest

The Authors have no conflicts of interest to disclose with respect to the publication of this paper.

Authors' Contributions

All Authors contributed to study conception and design. Data collection and analysis were performed by Moriyasu Yamauchi. The first draft of the manuscript was written by Moriyasu Yamauchi, and all Authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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