



Feasibility of Combination of Paclitaxel, Carboplatin, and Cetuximab as Induction Chemotherapy for Advanced Head and Neck Squamous Cell Carcinoma

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Abstract

Background/Objective: Combination of Docetaxel, Cisplatin, 5-FU (TPF) is regarded as the current standard regimen as induction chemotherapy for locally advanced Head and Neck Squamous Cell Carcinoma (HNSCC), but the problem is severe toxicity which occasionally causes treatment-related mortality. The current study examined feasibility of combination with Paclitaxel, Carboplatin and Cetuximab (PCE) as comparable regimen with less toxicity.

Materials and Methods: The efficacy and the adverse events of 2 cycles of PCE regimen were retrospectively examined for 40 cases with stage III/IV HNSCC using RECIST and CTCAE.

Results: Thirty-five cases (87.5%) completed 2 cycles of PCE therapy. Overall Response Rate (ORR) was 65%: 50% in oral and sinonasal cancers, 57% in laryngeal cancer, 87.5% in hypopharyngeal cancer, and 100% in oropharyngeal cancer. Infusion reaction and interstitial pneumonia occurred in one case for each. Neutropenia and febrile neutropenia occurred in 60% and 7.5%, respectively. Elderly were not significant factor of increased adverse events. All cases were successfully treated with definitive radiotherapy, chemoradiotherapy, or surgery following PCE. Two year overall and disease specific survival rates were 80% and 82.6%, respectively.

Conclusion: Induction therapy with PCE showed comparable effects to TPF with less toxicity. PCE is available in outpatient set-up even for elderly. Although the survival data is immature and the number of subjects is still small, it is suggested that PCE should be useful as induction chemotherapy for advanced HNSCC.

Keywords: Induction chemotherapy; Paclitaxel; Carboplatin; Cetuximab; Head and neck cancer; Efficacy

Introduction

Induction Chemotherapy (ICT) was reported by Frei et al. [1] in 1982 as Neo-Adjuvant Chemotherapy (NAC) for Head and Neck Squamous Cell Carcinoma (HNSCC), and it has been developed through Veterans Affairs (VA) study and TAX study [2-4]. The VA study compared induction chemotherapy with cisplatin and 5FU (PF) followed by Radiotherapy (RT) with total laryngectomy for stage III/IV laryngeal cancers and demonstrated that ICT+RT had same survival rates as laryngectomy with significantly higher laryngeal preservation. TAX study compared the effects of ICT with PF to ICT with TPF (PF plus Docetaxel) for HNSCC and revealed significantly higher survival rates in TPF group. Although the significant impact of the ICT has not been fully determined, ICT is clinically used for HNSCC expecting preservation of organ function [2,5,6], prevention of distant metastasis [2,5,7], and improvement of prognosis [8]. ICT is also used for chemoselection which can lead to organ preservation therapy [2,9,10].

Although TPF regimen is the current standard treatment for locally advanced HNSCC (LA-HNSCC) as induction chemotherapy, one of the significant problems is the severe toxicity, including febrile neutropenia and treatment related death of up to 5% [4]. Furthermore, TPF regimen is considered to be difficult to apply for the elderly due to the toxicities. The need to develop a regimen that has comparable efficacy to TPF with less toxicity has been warranted. To date, the cytotoxic drugs and the molecularly targeted agent are more frequently combined to avoid the overlap of the toxicities [11].

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Kies et al. [12] reported the efficacy of Paclitaxel/Carboplatin/Cetuximab (PCE) as ICT for HNSCC in 2010. The Overall Response Rate (ORR) in patients with measurable disease was 96% including CR in 19% and PR in 77%. Although PCE therapy showed higher efficacy as compared to TPF (about 70% ORR), the cases involved in the PCE study were mostly oropharyngeal carcinoma (87%). It is still unclear whether or not PCE is useful for various cancers in the head and neck, because it is well known that oropharyngeal cancer, particularly HPV positive cancer, is most sensitive to chemotherapy among HNSCC [4].

The current study retrospectively reviewed the feasibility of PCE therapy as induction chemotherapy for various cancer types in the head and neck regions by examining initial effects and safety aspect.

Materials and Methods

Patients

Chart review was completed for stage III/IV HNSCC patients who received PCE therapy as induction chemotherapy from 2017 to 2018. Patient demographics and clinical characteristics are shown in (Table 1). All the cases were histologically proven HNSCC. The cases were divided into 3 age groups which consisted of under 65 years of age, 65 to 74 years of age, and 75 years of age and older. Especially, 9 elderly cases over 75 years old were included in this study. T3 and T4 cases occupied 75%. The primary sites included oral cavity in 35% of the cases, oropharynx in 12.5%, hypopharynx in 22.5%, larynx in 20%, and paranasal sinus in 10%. All cases with oropharyngeal cancer were p16 negative.

Induction chemotherapy and response evaluation

The treatment schedule was modified from the regimen by Kies et al. [12]. Chemotherapy consisted of paclitaxel 100 mg/m² on days 1,8; carboplatin area under the blood Concentration-Time Curve (AUC) 2.0 on days 1,8, repeated every 3 weeks for up to 2 cycles; and Cetuximab at an initial dose of 400 mg/m² on day 1 followed by 250 mg/m² weekly up to the end of the chemotherapy. The initial dose of paclitaxel was reduced to 80 mg/m² in the patients who were over 75 years of age. The doses of paclitaxel and carboplatin were modified in cases of severe hematological or non-hematological toxicity: paclitaxel to -1 level (80 mg/m² or 60 mg/m²); carboplatin to -1 level (AUC, 1.5). Cetuximab was modified to -1/-2 level (200 mg/m², 150 mg/m²) in the case of severe skin rash. The PCE regimen was approved by institutional review board for chemotherapy regimen in Kyoto Prefectural University of Medicine.

Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 was used to evaluate the efficacy of ICT using Complete Response (CR); Partial Response (PR); Stable Disease (SD); and Progressive Disease (PD). The therapeutic effects were evaluated for each primary site.

Adverse events

Adverse events were coded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. The adverse events were compared according to ages.

Treatment after induction chemotherapy

After ICT, patients underwent the subsequent treatment, which consisted of radiotherapy with/without concurrent chemotherapy in 13 cases, organ preservation surgery in 21 cases, and extended surgery in 6 cases, according to the tumor status and the primary site (Figure 1). Chemoselection strategy was used for the cancers in the larynx

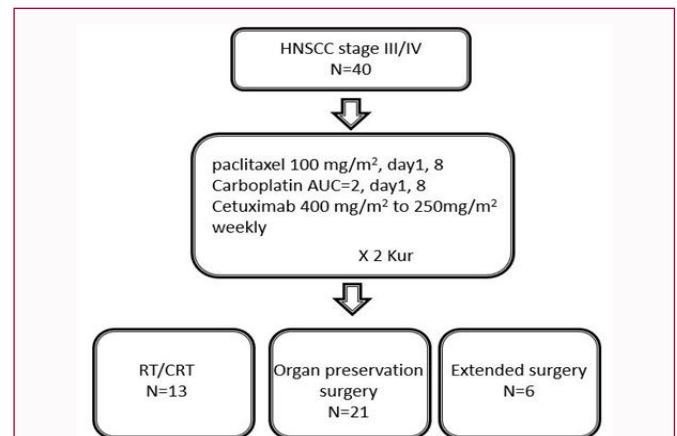


Figure 1: Scheme of treatment. Chemoselection strategy was used to determine the therapy following PCE.

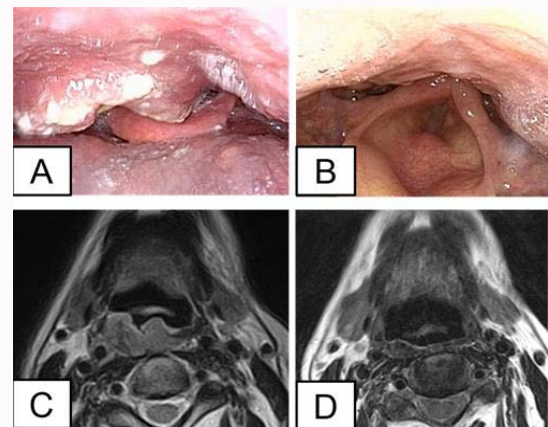


Figure 2: A representative case of CR. A,B: Endoscopic findings before and after PCE therapy. C,D: MRI findings before and after PCE therapy. The oropharyngeal cancer of posterior wall completely disappeared by PCE therapy.

and hypopharynx.

Statistical analysis

Relationship between age and neutropenia was analyzed using the Spearman's correlation coefficient by rank test and the Mann-Whitney *U* test. *p*<0.05 was considered to be statistically significant.

Results

Treatment compliance

Thirty-five (87.5%) patients completed 2 cycles of PCE. Five cases discontinued the chemotherapy because of adverse events including Infusion Reaction (IR) and anaphylaxis in one case, deterioration of general condition in one case, interstitial pneumonia in one case, and febrile neutropenia in 2 cases. Three of them completed one cycle of PCE. When the compliance was analyzed separately for less than 65 years of age, 65 to 74 years of age, and 75 years of age and older, the compliance rates were 83.3%, 89.4%, and 77.8%, respectively.

Efficacy

The efficacy of PCE is shown in (Table 2). Overall Response Rate (ORR) was 65% in 37 cases including 3 cases that achieved one cycle of PCE. The effect observed in the primary tumor was similarly observed in the cervical lymph nodes in most cases. Particularly, CR was confirmed in the both sites. A representative case of CR is

Table 1: Patients demographic data.

	n	%
Gender		
Male	30	75
Female	10	25
Age, years		
<65	12	30
≥ 65, <75	19	47.5
≥ 75	9	22.5
T		
T1	3	7.5
T2	9	22.5
T3	15	37.5
T4a	11	27.5
T4b	2	5
N		
N0	18	45
N1	6	15
N2b	8	20
N2c	3	7.5
N3b	5	12.5
Primary site		
Oral cavity	14	35
Oropharynx (p16-negative)	5	12.5
Hypopharynx	9	22.5
Larynx	8	20
Sinus	4	10

Table 2: Efficacy of PCE.

	n	CR	%	PR	%	SD	%	PD	%
Total cases	37	3	8.1	21	56.8	12	32.4	1	2.7
Oral cavity	14	0	0	7	50	7	50	0	0
Sinus	4	1	25	1	25	2	50	0	0
Larynx	7	1	14.3	3	42.9	3	42.9	0	0
Oropharynx	4	1	25	3	75	0	0	0	0
Hypopharynx	8	0	0	7	87.5	0	0	1	12.5

shown in (Figure 2). A 77-year-old man with oropharyngeal cancer demonstrated complete disappearance of the primary tumor both on the image and on the endoscopic examination. ORR for each primary site was 50% for oral and sinonasal cancer, 57% for laryngeal cancer, 100% for oropharyngeal cancer, and 87.5% for hypopharyngeal cancer (Table 2). Only case with PD was cT1N3b hypopharyngeal cancer, which indicated advancement of the cervical lymph node metastasis although the primary site was almost disappeared. The total RECIST defined PD in this case.

Adverse events

Adverse events are shown in (Table 3). Neutropenia and febrile neutropenia were found in 60% and 7.5% of the total cases, respectively. Anemia was found in over the half of the total cases. Grade 3/4 neutropenia was seen in 35%, and Grade 3/4 anemia was seen in 2.5%. Although PCE regimen contains CBDCA, adverse

Table 3: Adverse events.

	n	%	G3	%	G4	%
Hematologic						
Neutropenia	24	60	10	25	4	10
Febrile neutropenia	3	7.5	2	5	1	2.5
Anemia	23	57.5	1	2.5	0	0
Thrombocytopenia	6	15	0	0	0	0
Nonhematologic						
Skin rash	6	15	0	0	0	0
Hypomagnesemia	1	2.5	1	2.5	0	0
Interstitial pneumonia	1	2.5	0	0	0	0
Infusion reaction/allergy	2	5	1	2.5	0	0
Electrolyte abnormality	2	5	2	5	0	0
Liver disorder	7	17.5	1	2.5	0	0
Appetite loss	7	17.5	0	0	0	0
Diarrhea	2	5	1	2.5	0	0

Table 4: Occurrence of neutropenia due to age.

Age	G0	G1	G2	G3	G4
≥ 40, <49	2	0	2	0	0
≥ 50, <59	3	0	2	0	0
≥ 60, <69	5	0	1	5	2
≥ 70, <79	6	0	4	4	2
≥ 80, <89	0	0	1	1	0
Age	All grade	%	G3/4	%	
<65	6	50	1	8.3	
≥ 65, <75	11	57.9	8	42.1	
≥ 75	7	77.8	5	55.6	

events of thrombocytopenia were few in this study. Skin rash, hypomagnesemia, and interstitial pneumonia, which were unique side effects of cetuximab, were found in 15%, 2.5%, and 2.5% of the total cases, respectively. IR is also unique side effect of cetuximab, and allergic reaction is a unique side effect of PTX. One case with p16 negative oropharyngeal cancer showed the IR and anaphylaxis sequentially. Peripheral neuropathy, which is a unique side effect of PTX, was not found in this study. Severe nonhematologic adverse events of Grade 3/4 except for IR/anaphylaxis seemed few.

Correlation analysis between age and neutropenia showed more frequent neutropenia as the age was older (Table 4). However, there was no statistically significant correlation between age and neutropenia (Spearman’s correlation coefficient by rank test, p=0.16, Mann-Whitney U test, p=0.08).

Survival data

2-year Overall Survival (OS) and Disease Specific Survival (DSS) were 80% and 82.6%, respectively (Figure 3).

Discussion

PCE regimen was first reported by Kies et al. [12] as induction chemotherapy for LA-HNSCC in 2010. This study had impact in terms of the good efficacy with 95% ORR with decrease of toxicity, compared with TPF regimen. However, most cases in this study were oropharyngeal carcinoma which is the most favorable case to chemotherapy. Induction chemotherapy with PCE was reported

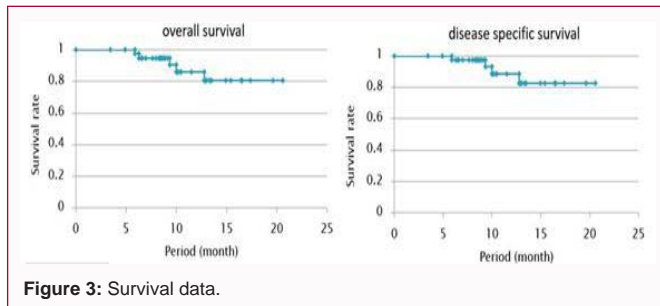


Figure 3: Survival data.

afterwards in a retrospective study by Bauman et al. [14] in 2013. Thirty cases were treated by PCE followed by chemoradiotherapy or surgery. Although survival data were not mature, PCE showed good response rate of 97% including CR for 30% of patients. Weiss et al. [15] reported combination therapy with paclitaxel, carboplatin, and lapatinib as neoadjuvant chemotherapy in phase II clinical trial in 2018. They showed high response rate of 93% including 36% pCR. In spite that these studies indicated high response rates of head and neck cancer to combination therapy of chemotherapy and molecular target agent, most cases were oropharyngeal cancer. In the current study, we evaluated the efficacy of PCE regimen for LA-HNSCC of various sites retrospectively. The results show that the therapeutic effects of PCE and TPF were comparable. The current PCE therapy worked well for both the primary tumor and lymph nodes metastasis in parallel in most cases.

The therapeutic effect by primary site in TPF regimen has been reported, and the current PCE seemed to have the similar effect by site to TPF [4]. It is well known that oropharynx best responds to induction chemotherapy, while the effects decrease for oral and sinus cancers. The current results indicate high response rates for oropharyngeal and hypopharyngeal cancers, which seem to be compatible to the notion. It also showed a therapeutic effect on p16 negative oropharyngeal cancer, which is believed to have less response to chemotherapy than p16 positive oropharyngeal cancer [16]. The current results are also compatible to the previous reports for PCE induction chemotherapy in terms of efficacy. The ORRs reported by Kies et al. [12] and Bauman et al. [14] were very high as 95% and 97%, respectively for the patients chiefly consisting of oropharyngeal cancer, and the current study also indicated 100% ORR for oropharyngeal cancer. Even though the efficacy rates for oral and sinus cancers were 50%, it can be interpreted that a half of the cases had benefits of ICT, while no PD case was observed.

PCE regimen had lower side effect than TPF regimen. In TAX324 study, Grade 3/4 neutropenia and febrile neutropenia induced by TPF regimen were 83% and 12% [4], while in this study, Grade 3/4 neutropenia and febrile neutropenia was 35% and 7.5%. In TPF regimen, treatment related death was reported as 5% [4]. Concurrent chemoradiotherapy using CDDP has been reported to be intolerable for the cases after TPF treatment. Our results show that there was only one case who could not receive planned cisplatin (CDDP) with radiotherapy after PCE therapy because of febrile neutropenia followed by acute renal failure. PCE regimen is thought to be safer which secures the following treatment option. Kies et al. [12] also reported 21% occurrence of grade 3/4 neutropenia without fever, and Bauman et al. [14] reported grade 3/4 toxicities as less than 7%.

The present results suggested that PCE regimen could be applied even for the elderly. Even though 2 cases older than 75

year discontinued the regimen due to IR/anaphylaxis in one and deterioration of general condition followed by bacterial pneumonia in another case, there was no significant correlation between age and IR and/or allergic reaction. There was no significant correlation between age and neutropenia, either.

The current study is a retrospective study with small number of cases, and only indicates initial effects of PCE without long-term survival results. Although such data will be necessary in the next step, it is suggested that PCE therapy is, at least, feasible for LA-HNSCC as induction chemotherapy in terms of initial effects and safety aspect.

Conclusion

We verified the efficacy and the safety aspects of PCE regimen as induction chemotherapy for HNSCC, retrospectively. The therapeutic effects of PCE and TPF seemed to be comparable and the adverse events were much lower in PCE than TPF. PCE regimen as induction chemotherapy seemed to be one of highly effective and safe chemotherapy regimens. Furthermore, even the elderly can be well tolerated for PCE. It is another benefit of PCE that it can be performed in outpatient setting. In conclusion, PCE regimen is considered to be useful as induction chemotherapy for LA-HNSCC.

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