Comprehensive Support Project

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)

福田裕次郎[1], 長谷川泰久[1], 鬼塚哲郎[2], 丹生健一[3], 川端一嘉[4], 岩江信法[5], 本間明宏[6], 鈴木政美[7], 家根旦有[8], 山中竹春[9], 田原　信[10]

[1]愛知県がんセンター中央病院　頭頸部外科; [2]静岡県立静岡がんセンター　頭頸部外科; [3]神戸大学医学部附属病院　耳鼻咽喉・頭頸部外科; [4]がん研究会有明病院　頭頸科; [5]兵庫県立がんセンター　頭頸部外科; [6]北海道大学病院　耳鼻咽喉科; [7]群馬県立がんセンター　頭頸科; [8]近畿大学医学部奈良病院　耳鼻咽喉科; [9]横浜市立大学医学部　臨床統計学; [10]国立がん研究センター東病院　頭頸部内科

第40回　日本頭頸部癌学会学術集会
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筆頭発表者名：　福田裕次郎

研究費：
メルクセローノ株式会社（MSJ）と公益財団法人パブリックヘルスリサーチセンター（CSPOR）の臨床研究プロジェクト契約に基づいてMSJから提供を受けた。

Background

- In EXTREME study, adding cetuximab to platinum-based chemotherapy (PF) demonstrated significantly improved survival over platinum-based chemotherapy alone [1].
- However, this regimen requires hospitalization to ensure proper hydration and continuous infusion of 5-FU, and causes concerned toxicities including mucositis, anorexia and fatigue, leading to worsen patient's quality of life.
- In the previous study for R/M SCCHN patients who received platinum-derivates, combination with paclitaxel, carboplatin and cetuximab (PCE) demonstrated promising clinical activity with response rate of 56% and median time to progression of 5 month [2].

1. Vermorken JB et al. N Engl J Med 2008; 359: 1116-1127.
2. Buentzel J, et.al. 2007 ASCO Annual Meeting. JCO, 2007; No. 18S (June 20 Suppl) abstr 6077.

Objectives

- To evaluate the efficacy and safety of PCE as first-line treatment in patients with R/M SCCHN.
  - Primary endpoint　; overall response rate (ORR)
  - Secondary endpoints; safety
    treatment completion rate
    progression-free survival
    overall survival
    clinical benefit rate (CBR)

Method

Patients

Key eligibility criteria:

1) Histologically proven squamous cell carcinoma
2) Primary lesion located larynx, oropharynx, hypopharynx or oral cavity
3) No prior chemotherapy expect > 6 month previous chemotherapy as a curative therapy
4) No prior systemic chemotherapy for recurrent/metastatic disease

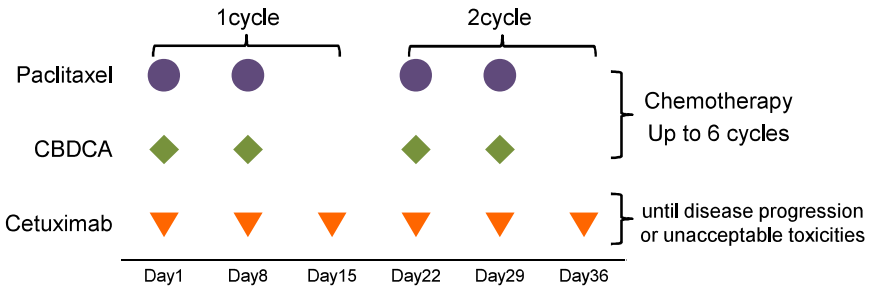
Study design

This is a single arm, open-label, multicenter, phase 2 study (UMIN000010507)

Treatment

Chemotherapy consisted of paclitaxel 100mg/m^2 on day 1, 8; carboplatin AUC 2.5 on day 1, 8, repeated every 3 weeks for up to 6 cycles; and cetuximab at an initial dose of 400mg/m^2, followed by 250mg/m^2 weekly until disease progression or unacceptable toxicities (Fig 1).

Fig.1



Assessment

- Tumor responses were assessed by CT or MRI at baseline and at 8-week intervals after the start of treatment until disease progression or treatment discontinuation.
- Adverse events were monitored weekly throughout the study and evaluated by CTCAE version 4.0.

Statistical analysis

- The objective of primary analysis is to confirm whether response rate of PCE is non-inferior as compared with that of PFE
  - Assumed the response rate of PFE is 40%
  - Acceptable range of less than 5%
- Targeted accrual: 45 patients in total

Results

Forty-seven subjects were accrued from July 2013 and Oct 2014.

Patient Characteristics (n=45)

Variable		No. of patients
Age		
	Age (yr) - median, range	63 (41-76)
	＜65yr	25
	≧65yr	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)
	non-smokers	9

Compliance

Median cycle of PCE was 6.

	Median duration-week (range)	Relative dose intensity %
Paclitaxel	16.9 (1.9 - 28.0)	82.5
CBDCA	7.1 (1.9 - 28.0)	82.5
Cetuximab	22.0 (2.0 - 128.0)	90.6
Cetuximab monotherapy*	11.9 (1.0 - 116.0)	90.6

*during the maintenance period

	No. of patients (%)
Completion of 6 cycles of PCE	16 (35.6%)
Received cetuximab monotherapy*	29 (64.4%)

*during the maintenance period

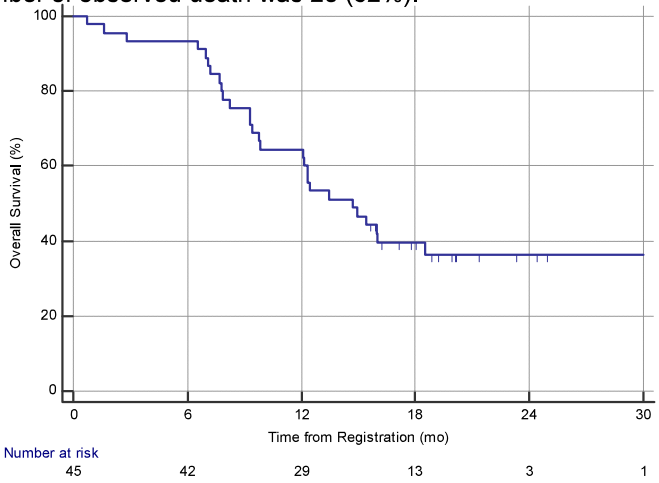
Analysis of primary endpoint
Response (N=45) on central review

The primary end point was met with ORR of 40.0%
(95% exact CI, 25.7-55.7).

Response	No. of patients (%)
Complete response	2 (4.4%)
Partial response	16 (35.6%)
Stable disease	9 (20.0%)
Progressive disease	16 (35.6%)
Not Evaluable	2 (4.4%)

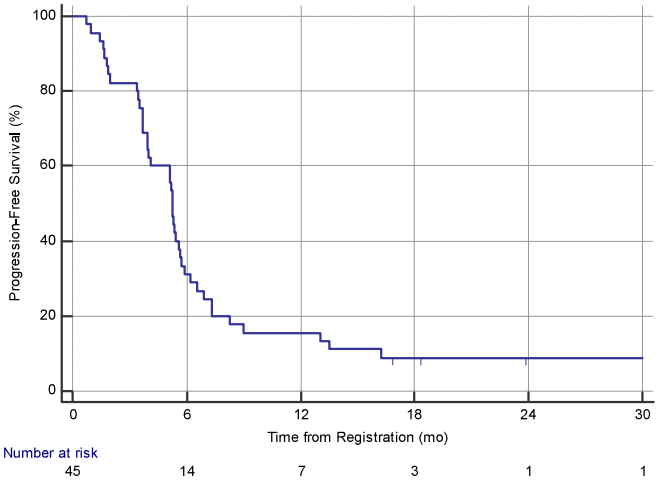
Overall survival

Median follow-up was 20.0 months.
Median overall survival was 14.7 months (95% CI, 9.8–Not Reached).
Number of observed death was 28 (62%).



Progression-free survival

Median progression-free survival was 5.2 months (95% CI 3.9–5.6).
5 patients are still receiving cetuximab maintenance.



Subsequent treatment

	No. of patients			
	2nd	3rd	4th	5th
Total (%)	32(68.1%)	14	5	2
S-1	13	1	2	0
Immunotherapy*	4	5	0	0
Docetaxel	3	4	0	0
Cmab	5	0	0	0
PXL+CBDCA	1	0	1	0
Others	2	2	1	2
Palliative RT	4	2	1	0

*anti-PD-1/PDL-1 antibody

Safety

Adverse events* during PCE (N=47)

AE	Gr1	Gr2	Gr3	Gr4	%Gr3-4
Neutropenia	2	9	19	13	68%
Rash acneiform	14	23	2	0	4%
Skin reaction#	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%
Hypoalbminemia	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%
Tbil increased	10	0	0	0	0%

*Grade1 or worse adverse events in 20% or more of patients, # Excluded rash acneiform
A potentially treatment-related death occurred in one patient with intestinal pneumonia.

Conclusion

- The PCE regimen shows promising activity with acceptable toxicity and can be provided in the outpatient clinic, with weekly adjustment of dosages according to toxicity. Further studies are needed to compare PCE with PFE in this population.

試験参加施設一覧					
1	国立がん研究センター東病院	頭頸部内科	13	国立病院機構東京医療センター	耳鼻咽喉科
2	近畿大学医学部奈良病院	耳鼻咽喉科 歯科口腔外科 腫瘍内科	14	奈良県立医科大学附属病院	耳鼻咽喉・頭頸部外科 腫瘍センター
3	近畿大学医学部附属病院	腫瘍内科 耳鼻咽喉科	15	がん研究会有明病院	総合腫瘍科 頭頸科
4	北海道大学病院	耳鼻咽喉科	16	愛知県がんセンター中央病院	頭頸部外科 放射線治療部 薬物療法部
5	岩手医科大学附属病院	血液腫瘍内科 耳鼻咽喉科・頭頸部外科	17	静岡県立静岡がんセンター	消化器内科 頭頸部外科 原発不明
6	東北大学病院	腫瘍内科	18	兵庫県立がんセンター	腫瘍内科 頭頸部外科
7	千葉県がんセンター	腫瘍・血液内科 頭頸科 外来科学療法科	19	東海大学医学部付属病院	耳鼻咽喉科
8	群馬県立がんセンター	頭頸科 呼吸器内科	20	神戸大学医学部附属病院	腫瘍・血液内科 耳鼻咽喉・頭頸部外科 放射線腫瘍科
9	京都大学医学部附属病院	耳鼻咽喉科 放射線治療科 がん薬物治療科	21	東京慈恵会医科大学附属病院	耳鼻咽喉科
10	埼玉県立がんセンター	消化器内科 放射線治療科 頭頸部外科	22	神奈川県立がんセンター	頭頸部外科 腫瘍内科
11	大阪市立総合医療センター	臨床腫瘍科 耳鼻咽喉科	23	自治医科大学附属病院	臨床腫瘍科 耳鼻咽喉科 歯科口腔外科
12	宮城県立がんセンター	頭頸部外科	24	四国がんセンター	頭頸科 呼吸器内科