Abstract No.6071

A Multicenter Phase II Trial of Docetaxel, Cisplatin and Cetuximab (TPE) Followed by Cetuximab with Concurrent Radiotherapy in Patients with Local Advanced Squamous Cell Carcinoma of the Head and Neck (ECRIPS study)

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Comprehensive Support Project

Abstract

Background

Induction chemotherapy followed by chemo-radiotherapy is a promising treatment option for locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). Docetaxel, Cisplatin, and 5-FU (TPF) followed by high-dose Cisplatin with radiotherapy is currently not recommended due to toxicity concerns. The aim of this phase II study was to assess the feasibility of Docetaxel, Cisplatin, and Cetuximab (TPE) followed by Cetuximab with concurrent radiotherapy for LA-SCCHN.

Methods

Patients were eligible if they had histologically proven SCC of oropharynx, hypopharynx or larynx, a PS of 0-1, adequate organ function, and no distant metastasis. Induction chemotherapy consisted of Cisplatin 75mg/m^2 and Docetaxel 75mg/m^2 on day1 and the induction regimen was repeated every 3 weeks up to a total of 3 courses. Cetuximab was administered at an initial dose of 400mg/m^2 followed by 250mg/m^2 weekly until the end of radiotherapy. Radiotherapy (70Gy/35fr/7w) was started after last administration of Docetaxel. Primary endpoint was the rate of treatment completion. Treatment completion was defined by receiving i) induction chemotherapy of 2 or more courses, ii) radiotherapy within 6 weeks from the last dose of the induction therapy, iii) full dose radiotherapy, and iv) Cetuximab of more than 12 times. The planned sample size was 55 with one-sided alpha of 0.025 and the power of more than 90% based on the expected and threshold treatment completion rates of 65% and 40%

Results

Between August 2013 and October 2015, 54 patients with a median age of 58 years were eligible and had the study treatment. There were 50 males, hypopharynx/oropharynx/larynx cancer of 28/19/7 cases, and 48 Stage IV disease. Response rate at induction chemotherapy was 72% with a CR rate of 16% while that after radiotherapy was 76% with a CR rate of 48%. Of 54 patients, 50 (93%) received >2 courses of induction chemotherapy, 44 (81%) were administered cetuximab >12 times, and 41 (76%) had the full dose of radiotherapy. The rate of treatment completion was thus 76% (95%CI, 62–87%). The frequency of grade 3-4 neutropenia, febrile neutropenia, and allergy/infusion reaction was 93%, 39%, and 11%, respectively. One treatment-related death was observed.

Conclusion

Induction TPE followed by Cetuximab with concurrent radiotherapy was feasible with a promising efficacy. A phase III study to evaluate this treatment strategy is warranted.

Clinical trial information: UMIN000009928

Introduction

- Induction chemotherapy followed by chemo-radiotherapy is a promising treatment option for locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).
- Docetaxel, Cisplatin, and 5-FU (TPF) is the standard regimen as an induction chemotherapy
- On the other hand, TPF followed by high-dose Cisplatin with radiotherapy is currently not recommended due to toxicity concerns.
- Adding 5-FU on TP is toxic but may not effective, and Cetuximab with radiotherapy may be better partner for strong induction chemotherapy

The aim of this phase II study

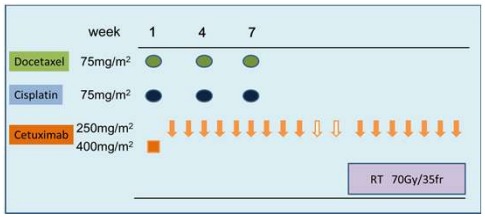
- To assess the feasibility of Docetaxel, Cisplatin, and Cetuximab (TPE) followed by Cetuximab with concurrent radiotherapy for LA-SCCHN.

Eligibility Criteria

- SCC of Oropharynx, hypopharynx and Larynx
- Stage III-IV (TNM 7th edition) Locally advanced resectable disease
- Age 20-75 years old
- PS0-1

Treatment Schedule

Docetaxel/CDDP/Cetuximab followed by Cetuximab with Radiotherapy



Endpoints and Statistical analysis

Primary Endpoint Treatment Compliance

Definition of completion of treatment
1. Induction chemotherapy (≥ 2 course)
2. The interval between last ICT and start of RT(<6weeks)
3. Full dose irradiation within 70days
4. Cetuximab administration (≥ 12 times)

The primary endpoint was treatment completion rate. Expected and threshold values for exact binomial test were 40% and 65% and a total of 55 was needed with a power of 90% and one-sided significance level of 2.5%

Patient characteristics

Age (Range)		58(35-72)
Gender	Male / Female	49 / 5
PS	0 / 1	42 / 12
Primary site	Oropharynx	19
	(P16+)	14 (73.7%)
	Hypopharynx	28
	Larynx	7

One case was excluded from full analysis set because it was found out not to meet eligibility criteria after registration

Induction phase / Radiotherapy phase

Treatment Compliance

Treatment Compliance

3 courses	44 (81.5%)
Full dose	23 (42.6%)
2 courses	6 (10.2%)
1 courses	4 (7.4%)

Relative Dose Intensity

Docetaxel	0.90 (0.86-0.94)
CDDP	0.84 (0.80-0.88)

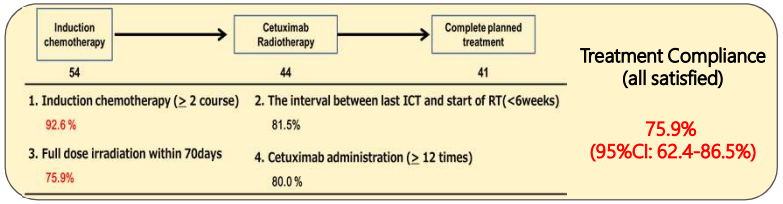
The reasons of treatment interruption

Toxicities 7 (Allergy 4, Infusion reaction 2, Sepsis 1), PD 2, Other reasons 1(Duodenal ulcer 1)

Patients No. of start irradiation	44 (44/54 81.5%)
The rate of full dose irradiation	41/44(93.2%)
Median RT dose (range)	70(66-70) Gy
Median RT duration (range)	51(45-60) days

The reasons of treatment interruption

Protocol deviation 1, Local infection 1, Sepsis 1



Toxicities at induction phase

(n=54)

	Grade (CTCAE ver.4.0) 1	2	3	4	% 3-4
Neutropenia	0	2	15	35	93
Platelet	25	4	0	0	0
Anemia	36	11	4	1	9
Nausea	5	1	0	0	0
Anorexia	17	18	4	0	7
Mucositis	15	11	3	0	6
Skin Rush	24	21	2	0	4
Infusion reaction	0	4	2	1	6
Allergy	0	2	4	1	9
Febrile neutropenia	0	0	20	1	39

Toxicities at radiotherapy phase

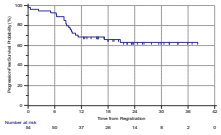
(n=44)

	Grade (CTCAE ver.4.0) 1	2	3	4	% 3-4
Neutropenia	7	2	0	0	0
Platelet	10	0	0	0	0
Anemia	28	11	3	0	0
Nausea	5	2	0	0	0
Anorexia	15	11	6	0	14
Mucositis	2	22	20	0	45
Skin Rush	22	16	2	0	5
Radiation Dermatitis	2	18	21	0	48
Infusion reaction	0	0	0	0	0
Allergy	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0

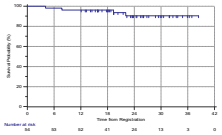
Response rate and Survival

	Induction phase		Radiotherapy phase	
CR	9	16.7%	26	48.1%
PR	30	55.6%	15	27.8%
SD	5	9.3%	0	0%
PD	1	1.9%	1	1.9%
NE	9	16.7%	12	22.2%

Progression Free Survival
2-year progression free survival: 64.3%



Overall Survival
2-year overall survival: 90.6%



Summary and Conclusion

Induction TPE followed by Cetuximab with concurrent radiotherapy was feasible with a promising efficacy.
A phase III study to evaluate this treatment strategy is warranted.

Acknowledgement

- The authors thank all the patients, study investigators, and clinical study teams(ECRIPS).

The following hospitals participated in this study.

National Cancer Center East, Tokai University, Kyoto University, Kobe University, Jichi Medical University, Jikei University, Tokyo Medical Center, Shizuoka Cancer Center, Aichi Cancer Center, Cancer Institute Hospital of JFCR, Hyogo Cancer Center, Hokkaido University , Hirosima University, Kobe City Medical Center, Kinki University , Shikoku Cancer Center, Nara Medical University, Chiba Cancer Center, Yokohama City University School of Medicine,

Funding

This study was funded by the Comprehensive Support for Oncology Research (CSPOR) of the Public Health Research Foundation. The research fund was provided to CSPOR by Merck Serono.