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Clinical Trial Results

Cisplatin/Tegafur/Uracil/Irinotecan Triple Combination Therapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: A Phase I/II Clinical Study

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Trial Information

- **ISRCTN Identifier:** ISRCTN17533723
- **Sponsors:** Taiwan Clinical Oncology Research Foundation and TYY Biopharma, Taipei, Taiwan, Republic of China
- **Principal Investigator:** Muh-Hwa Yang
- **IRB Approved:** Yes

Lessons Learned

- Cisplatin/tegafur/uracil/irinotecan triple combination therapy shows moderate response, especially in patients without previous chemoradiotherapy within the 6 months before this combination therapy.
- Toxicity is tolerable, and quality of life is improved in responders.

Abstract

Background. The prognosis is poor in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Triple combination therapy may increase tumor response.

Methods. This phase I/II prospective trial first determined the dose-limiting toxicity and recommended dose of irinotecan with cisplatin and tegafur/uracil (UFUR) in phase I. Irinotecan was supplied at doses of 40, 50, 60, and 70 mg/m^2 by using a standard 3+3 design. Doses of cisplatin and UFUR were held stable. In phase II, the recommended dose of irinotecan was administered intravenously (i.v.) over 90 min on day 1, with cisplatin 50 mg/m^2 i.v. over 60 min also on day 1, and oral UFUR 200 mg twice a day for 5 days every 2 weeks a cycle.

Results. In the phase I portion, 14 patients were enrolled, and the dose level of irinotecan at 60 mg/m^2 was defined as the recommended dose for the phase II portion of the study. Among 43 patients enrolled in the phase II portion, complete response was seen in 2 patients (4.7%) and partial response in 10 patients (23.3%), and the disease control rate was 39.5%. In a subgroup analysis of patients whose prior chemoradiotherapy was more than 6 months earlier, a response rate of 40.7% and disease control rate of 59.3% were observed.

Conclusion. Cisplatin/UFUR/irinotecan triple combination therapy is tolerated and effective for selected patients. Individualized choice of treatment will influence prognosis and quality of life in R/M HNSCC patients. ***The Oncologist*** 2016;21:537–538h

Discussion

HNSCC, the sixth most common cancer in the world, has the median overall survival of approximately 8 months. Even in the current era of monoclonal anti-epidermal growth factor receptor therapy, the addition of cetuximab to the most common platinum-fluorouracil chemotherapy only improved survival by approximately 3 months. In addition, cost-effectiveness issues are concerning. In Taiwan, cisplatin/fluorouracil (5-FU) is still the most common regimen for R/M HNSCC.

Recently, triple combination therapy in the induction setting for locally advanced HNSCC has shown a high response rate. Therefore, triple combination regimens were examined in R/M HNSCC. However, the continuous 96-hour infusion of 5-FU is inconvenient for patients. An oral 5-FU prodrug, UFUR, combined with cisplatin has demonstrated similar activity as continuous-infusion 5-FU in R/M HNSCC. In addition, the combination of irinotecan and cisplatin showed a synergistic anticancer effect. Hence, we conducted this phase I/II trial to

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test the efficacy and safety of the cisplatin/UFUR/irinotecan triple combination regimen.

In the phase I portion of the study, dose-limiting toxicity (DLT) developed in 2 of 5 patients (one had grade 3 nausea and vomiting, and the other had grade 3 febrile neutropenia) when the dose level of irinotecan was titrated to 70 mg/m^2. Therefore, 60 mg/m^2 was defined as the recommended dose. In the phase II portion of the study, the targeted response rate was 13 of 43 patients according to the study design, so that with 12 patients with partial or complete response the primary endpoint was not met. We found among patients with recurrence within 6 months of concurrent chemoradiotherapy (CCRT), only 1 patient (6.3%) had a partial response. However, of 27 patients who did not receive CCRT in the 6 months before entering this trial, 11 patients (40.7%) had objective response and 16 (59.3%) had disease control. The maximum change from baseline in the sum of target lesions is shown in the waterfall plot (Fig. 1). The median progression-free survival (PFS) was 3.2 months (2.7–6.4 months) and overall survival (OS) was 6.7 months (4.2–10.0 months). Patients who had no CCRT in the preceding 6 months had a longer median PFS of 3.8 months (2.5–8.0 months) and longer OS of 8.4 months (4.7–12.1 months).

The triple combination in our study did not result in a high level of toxicities. Grade 3/4 neutropenia developed in 12 (27.9%) patients, and only 1 (2.3%) had febrile neutropenia. The other common adverse events included diarrhea, nausea, and vomiting, which were in line with expectations due to the known safety profile of these three drugs. We also found the quality of life (QoL) was improved in patients who had response, which highlights the importance of patient selection.

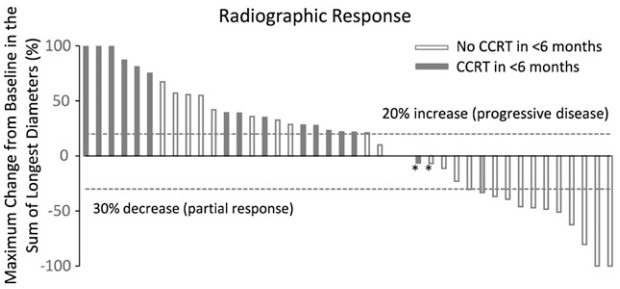

Figure 1. Change in tumor burden. Waterfall plots show the maximum change from baseline in the sum of target lesions (n = 42). ∗, With new onset of bone metastasis.
Abbreviation: CCRT, concurrent chemoradiotherapy.

In summary, cisplatin/UFUR/irinotecan triple combination therapy has tolerable toxicities and promising efficacy in the subset of R/M HNSCC patients without CCRT within 6 months of administration. The overall response is similar to other combination chemotherapies without associated increases in toxicity. However, selection of patients who are more responsive to this regimen to improve QoL remains an important issue.

Trial Information

Disease	Head and Neck Cancers
Stage of disease / treatment	Metastatic/Advanced
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Disease control rate
Secondary Endpoint	Quality of life
Secondary Endpoint	Toxicity

Additional Details of Endpoints or Study Design
Patients were eligible if they were aged 20 to 75 years, had histologically or cytologically confirmed nonnasopharyneal HNSCC, with locoregional recurrence after curative local treatment unsuitable for further local treatment, or primary distant metastasis at diagnosis, or metastatic disease after primary local treatment. No prior primary chemotherapy for metastatic disease was permitted. Previous induction or concurrent chemotherapy (CCRT) with primary radiotherapy or adjuvant therapy after curative surgery was allowed, but the chemotherapy regimen must have been completed at least 3 months before study entry. At least one measurable disease site was required, defined as a lesion measured in at least 1 dimension as ≥20 mm with conventional technique or ≥10 mm with spiral computed tomography (CT) scan or magnetic resonance imaging (MRI). Patients must have had a life expectancy of at least 12 weeks.

The main exclusion criteria were attributed to time since previous radiotherapy (less than 4 weeks) or previous major surgery (2 weeks). Other exclusion criteria included presence of central nervous system metastasis; bone-only metastasis; coexistence with other malignancy, with the exception of curatively treated nonmelanoma skin cancer or cervical carcinoma in situ within 5 years before entry into study; inadequate hematologic function (hemoglobin <8 mg/dL, white blood cells <3,000 per mm^3, absolute neutrophil count <1,500 per mm^3, and platelets < 100,000 per mm^3); inadequate hepatic function (serum bilirubin >1.5 times the upper limit [ULN] or alanine aminotransferase or aspartate aminotransferase > 2.5 times ULN if no liver metastasis or greater than 5 times the normal); inadequate renal function (serum creatinine > 1.5 mg/dL and creatinine clearance less than 60 mL/min); and concurrent treatment with other investigational drugs. This study has been fully reviewed by the institutional review board of Taipei Veterans General Hospital (VGHTPE-IRB: 2010-01-004MB).

The study comprised phase I and II components. The phase I study was a standard 3 + 3 dose escalation design. Irinotecan was to be administered in doses of 40, 50, 60, and 70 mg/m^2 in 3 patient cohorts and then escalated with 5 mg/m^2 increments until a DLT occurred. Irinotecan was administered intravenously (i.v.) over 90 min on day 1, with cisplatin 50 mg/m^2 i.v. over 60 min on day 1 and

oral UFUR 200 mg twice a day after meals (400 mg/day) for 5 days every 2 weeks. The maximum tolerated dose was established as one dose level below the dose associated with DLTs in more than one third of the patients in phase I, and was the recommended dose used in the subsequent phase II study. In the phase II study, a Simon's optimal two-stage design with $P_0 = 0.20$ and $P_1 = 0.40$, for which α and β error are 0.05 and 0.20, respectively, was used as a statistical guideline. If response was elicited from more than 13 responders from the 43 evaluable patients, the regimen was predicted to be efficacious.

The primary endpoint of the phase I study was determination of a recommended dose of irinotecan when combined with cisplatin and UFUR in patients with recurrent or metastatic HNSCC, by monitoring the DLT at each dose level. In the phase II study, the primary endpoint was the overall objective response rate of irinotecan in combination with cisplatin and UFUR. Tumor assessments were made by using CT or MRI scans at enrollment and every 3 months until disease progression or withdrawal. The revised RECIST guideline (version 1.1) was used to evaluate tumor response. Secondary endpoints were PFS, disease control rate, OS, QoL, and safety profile.

Adverse events and laboratory abnormalities were assessed in all patients by the National Cancer Institute Common Toxicity Criteria (version 4.0). DLT is defined as any of the following experiences during the first cycle: any grade 3/4 nonhematological toxicity (except alopecia), grade 4 thrombocytopenia, febrile neutropenia (fever $\geq$ 38.0°C with concomitant grade 3/4 neutropenia in the absence of documented infection), grade 3/4 infection, grade 4 neutropenia $\geq$ 6 days, or grade 3/4 neutropenia associated with severe infection. Severe adverse events were defined as any untoward medical occurrence, such as death, a life-threatening event, required inpatient hospitalization or prolonged existing hospitalization, persistent or significant disability or incapacity, and required medical intervention to prevent permanent impairment or damage. QoL was assessed by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) and H&N35 (EORTC-QLQ-H&N35) at each time point.

Descriptive statistics were calculated to characterize the patients. PFS and OS were estimated by the Kaplan-Meier method. QoL was scored on a 0–100 scale by the EORTC-QLQ-C30 and -H&N35 standards. A paired Student's *t* test was used to compare the score before and after the treatment. A p value $<.05$ was defined as statistically significant.

Investigator's Analysis	Correlative endpoints not met but clinical activity observed

Drug Information

Drug 1	
Generic/Working name	Irinotecan
Trade name	Irino
Company name	TTY
Drug type	Topoisomerase I inhibitor
Drug class	Topoisomerase I
Dose	60 mg/m^2
Route	i.v.
Schedule of Administration	Irinotecan was to be administered at doses of 40, 50, 60, and 70 mg/m^2 in each 3 patient step, and then escalated with 5 mg/m^2 increments until DLT occurred. The recommended dose in the phase I study was used in the subsequent phase II study. Irinotecan was administered intravenously (i.v.) over 90 min on day 1 every 2 weeks a cycle.
Drug 2	
Generic/Working name	Cisplatin
Drug type	Platinum compound
Drug class	Platinum compound
Dose	50 mg/m^2
Route	i.v.
Schedule of Administration	Cisplatin was supplied with the dose of 50 mg/m^2 i.v. over 60 min on day 1 every 2 weeks a cycle.
Drug 3	
Generic/Working name	Tegafur/uracil
Trade name	UFUR
Company name	TTY
Drug type	Small molecule
Drug class	Antimetabolite
Dose	200 mg per flat dose
Route	oral (po)
Schedule of Administration	UFUR was given with the dose of 200 mg twice a day for 5 days every 2 weeks a cycle.

Patient Characteristics

Number of patients, male	42
Number of patients, female	1
Stage	Recurrence or metastasis
Age	Median (range): 55 (26–74)
Number of prior systemic therapies	Median (range): Not Collected
Performance Status: ECOG	0 — 18 1 — 25 2 — 3 — unknown —
Cancer Types or Histologic Subtypes	Oral cavity, 20 Oropharynx, 11 Hypopharynx, 7 Larynx, 5

Primary Assessment Method

Control Arm: Total Patient Population	
Number of patients enrolled	43
Number of patients evaluable for toxicity	43
Number of patients evaluated for efficacy	43
Response assessment CR	*n* = 2 (4.7)
Response assessment PR	*n* = 10 (23.3)
Response assessment SD	*n* = 5 (11.6)
Response assessment PD	*n* = 26 (60.5)
Response assessment OTHER	*n* = 0 (0)
(Median) duration assessments PFS	3.2 months
(Median) duration assessments OS	6.7 months

Adverse Events

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All grades
Neutrophil count decreased	65%	14%	14%	5%	2%	0%	35%
Anemia	33%	44%	21%	2%	0%	0%	67%
Platelet count decreased	91%	9%	0%	0%	0%	0%	9%
Febrile neutropenia	100%	0%	0%	0%	0%	0%	0%
Fever	100%	0%	0%	0%	0%	0%	0%
Dysphagia	88%	7%	5%	0%	0%	0%	12%
Oral pain	82%	14%	2%	2%	0%	0%	18%
Dry mouth	83%	12%	5%	0%	0%	0%	17%
Nausea	66%	16%	16%	2%	0%	0%	34%
Vomiting	79%	7%	12%	2%	0%	0%	21%
Diarrhea	88%	5%	5%	2%	0%	0%	12%
Constipation	81%	12%	7%	0%	0%	0%	19%
Mucositis oral	100%	0%	0%	0%	0%	0%	0%
Dyspnea	95%	5%	0%	0%	0%	0%	5%
Anorexia	81%	12%	7%	0%	0%	0%	19%
Cough	81%	9%	5%	5%	0%	0%	19%
Fatigue	84%	9%	7%	0%	0%	0%	16%
Insomnia	86%	7%	7%	0%	0%	0%	14%
Abdominal pain	98%	2%	0%	0%	0%	0%	2%
Aspartate aminotransferase increased	98%	2%	0%	0%	0%	0%	2%
Alanine aminotransferase increased	93%	5%	2%	0%	0%	0%	7%

Hyperglycemia	98%	2%	0%	0%	0%	0%	2%
Hyponatremia	81%	19%	0%	0%	0%	0%	19%
Hypokalemia	93%	7%	0%	0%	0%	0%	7%

Adverse Events Legend
Adverse events in phase II study
*No Change from Baseline/No Adverse Event

Serious Adverse Events

Name	Grade	Attribution
Pneumonia	3	Unrelated
Poor wound healing	2	Unrelated
Pneumothorax	2	Unrelated
Sinusitis	3	Unrelated
Pneumonia	3	Unrelated
Nausea and vomiting	3	Probable
Nausea and vomiting	3	Probable
Sinusitis	3	Possible
Fatigue	3	Probable
Nausea and vomiting	3	Probable
Nausea and Vomiting	3	Probable

Serious Adverse Events Legend
Severe adverse events in phase I and II study

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics/Pharmacodynamics	Not Collected
Investigator's Assessment	Correlative endpoints not met but clinical activity observed

For recurrent/metastatic HNSCC, the prognosis is poor. Even in the current era of monoclonal anti-epidermal growth factor receptor (EGFR) therapy, Vermorken et al. [1] found that addition of cetuximab to the most common platinum-fluorouracil chemotherapy only improved survival by approximately 3 months. Although this cetuximab/platinum/5-FU therapy has made substantial progress for R/M HNSCC for recent decades, cost-effectiveness issues are concerning, especially in developing countries [2]. In Taiwan, cisplatin/fluorouracil (PF) is still the most common regimen for R/M HNSCC.

Recently, in response to the success of the triple combination therapy of cisplatin/docetaxel/infusional 5-FU in the induction setting for locally advanced HNSCC [3, 4], there were trials performed to examine such combination regimens in R/M HNSCC. The results showed that overall response could be achieved in up to 40%, but grade 3/4 toxicities were concerning [5]. Additionally, the continuous 96-hour infusion of 5-FU is inconvenient, raising the question of whether alternative schedules or formulations could be comparable. An oral 5-FU prodrug, tegafur/uracil, has been found to have similar activity in combination with cisplatin for R/M HNSCC [6].

Irinotecan, an analog of camptothecin that inhibits topoisomerase I, has high-potency antitumor activity [7]. In R/M HNSCC, the single use of irinotecan has demonstrated a modest overall response rate of 21.2%, and the combination of irinotecan and cisplatin is also effective [8]. To test the efficacy and safety of the cisplatin/UFUR/irinotecan triple combination regimen, we conducted a phase I/II trial to establish the dose-limiting toxicities, maximum tolerated dose (MTD), efficacy, and tolerability for patients with R/M HNSCC.

Between February 19, 2010, and July 9, 2015, a total of 14 patients were enrolled in the phase I study, and 43 patients were enrolled into the phase II study (Table 1). This phase I/II study defined the recommended dose of irinotecan at 60 mg/m^2 in the triple combination with cisplatin and UFUR, which had a modest response rate in R/M HNSCC, especially in those who had no CCRT in the 6 months before study entry (Table 2; Fig. 2).

The combination of platinum and fluorouracil was reported nearly 20 years ago to have a response rate of 20%–30% [9, 10]. In recent years, Vermorken et al. and Gibson et al. have described the response rates at 29% and 20%, respectively, with the same combination, which confirms the results of previous studies [1, 11]. In our study, we attempted to increase the response with the addition of irinotecan to this combination, but the response rate was similar. This might be explained by the difference in inclusion criteria between the studies. In previous studies, patients were excluded if they had received chemotherapy in the 6 months before entering the trials [1, 11]. Generally, patients with early recurrence after chemotherapy are considered more likely to have chemo-resistance than those with late recurrence. Hence, we performed a subgroup analysis, which showed the response rate of 40.7% and 34.6% in patients who had no CCRT or no CT within the previous 6 months, respectively. In this case, the efficacy of our combination appears to be comparable with the combination of cetuximab plus platinum–fluorouracil, which had a response rate of 36% in the Extreme study [1]. In

addition, nearly 76.8% of patients in our study had experienced chemotherapy, compared with only 26% in the other study [1]. Although our study did not meet the planned primary endpoint for efficacy (13 of 43 patients), this combination regimen may still have promising activity in selected patients.

The triple combination in our study did not result in a high level of toxicities (Table 3). Some adverse events—including anemia, dysphagia, dyspnea, hoarseness, and cough—were considered more likely to be associated with underlying disease, because these events developed in patients before their entry into this clinical trial. Grade 3/4 neutropenia developed in 12 (27.9%) patients, and only 1 (2.3%) had febrile neutropenia, which was similar in incidence with the previous study [1]. Other common adverse events, including diarrhea, nausea, and vomiting, were in line with expectations due to the known safety profile of these three drugs. In a previous study, Gilbert et al. demonstrated some efficacy of the combination cisplatin and irinotecan, but toxicity restricted its routine use [8]. To compare with their regimen, we used a lower dose of irinotecan, but added one more agent, UFUR, a combination that proved to have a similar response with tolerable toxicity. Another concern is that our regimen only improved QoL in patients who had a response. The improvement of QoL may be attributed to tumor control, which also highlights the importance of patient selection (Tables 4, 5).

A limitation of this study is the lack of prestudy investigation regarding polymorphisms of uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1), which is associated with irinotecan metabolism and drug-related toxicities [12]. With polymorphism information, the dosage could be decreased in high-risk patients to avoid severe adverse events, or it could be increased in low-risk patients to achieve a better response. However, the occurrence of the high-risk polymorphism is relatively rare in the Taiwan population compared with that in Caucasians [13]. Hence, the associated toxicity of this polymorphism was unlikely to be observed in this study because of the low incidence and limited population.

In conclusion, cisplatin/UFUR/irinotecan triple combination therapy has a similar efficacy with other combination chemotherapies. In selected patients, the efficacy was promising, with improving QoL and tolerated toxicities. Further investigation of this combination in patients who have not received CCRT within 6 months would be warranted.

Disclosures

The authors indicated no financial relationships.

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Figures and Tables

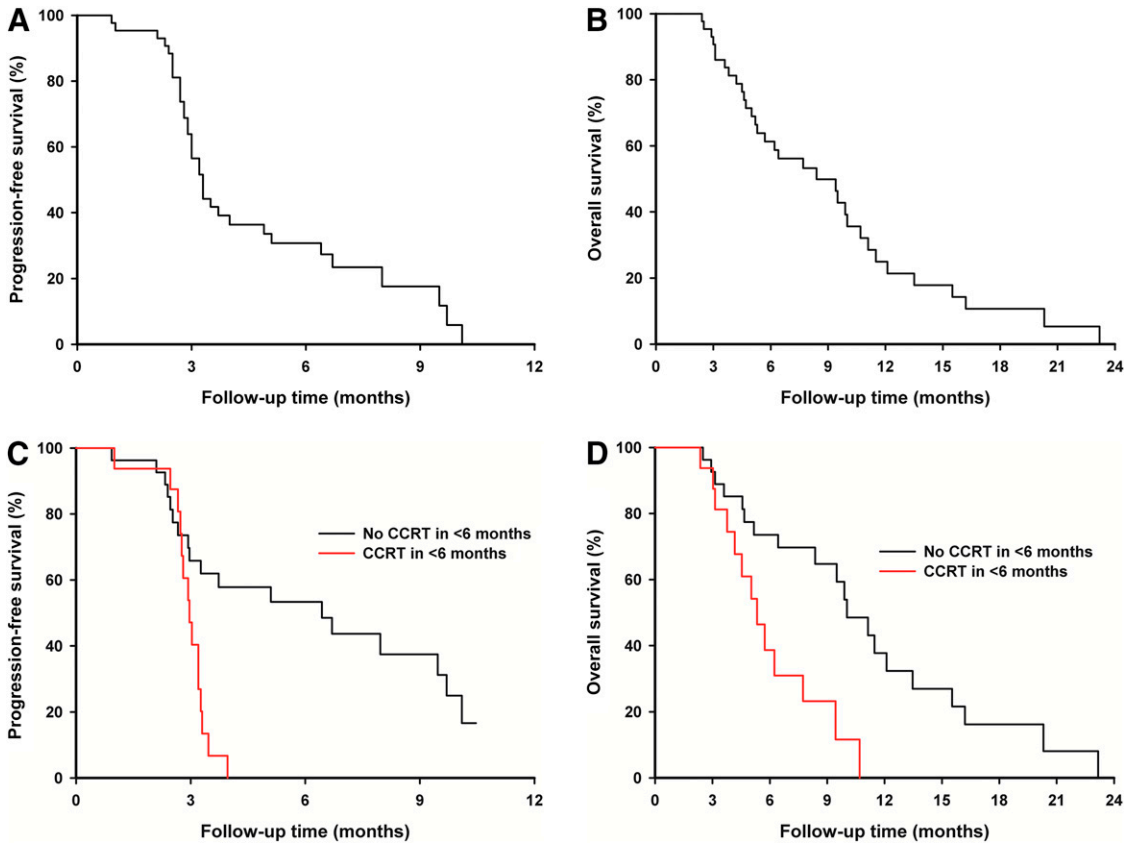

Figure 2. Kaplan-Meier analysis of study population. **(A)**: Progression-free survival in all cases. **(B)**: Overall survival in all cases. **(C)**: Progression-free survival between cases with/without CCRT in 6 months (median, 3.0 vs. 3.8 months; $p = .002$). **(D)**: Overall survival between cases with/without CCRT in 6 months prior (median, 5.1 vs. 8.4 months; $p = .002$).

Abbreviation: CCRT, concurrent chemoradiotherapy.

Table 1. Patient characteristics

	Phase I ($n = 14$)		Phase II ($n = 43$)	
Characteristic	***n***	**%**	***n***	**%**
Age (mean ± SD)	54.9 ± 10.3		53.3 ± 9.6	
Male	14	100	42	97.7
Primary site				
Oral cavity	5	35.7	20	46.5
Oropharynx	5	35.7	11	25.6
Hypopharynx	3	21.4	7	16.3
Larynx	1	7.1	5	11.6
Extent of disease at the study entry				
Locoregional recurrence	4	28.6	12	27.9
Metastasis after local treatment	10	71.4	27	62.8
Metastasis at initial diagnosis	0	0	4	9.3
Number of metastatic sites				
0	4	28.6	12	27.9
1	10	71.4	20	46.5
2 or more	0	0	11	25.6
Previous therapy				
No	0	0	3	7.0
Surgery	14	100	19	44.2
Radiotherapy	14	100	37	86.0
5-Fluoropyrimidine	14	100	33	76.7
Platinum	14	100	32	74.4
Cetuximab	4	28.6	9	20.9
Taxanes	3	21.4	13	30.2

Table 2. Phase II response

	No previous CCRT in < 6 m ($n = 27$)		Previous CCRT in < 6 m ($n = 16$)		All ($n = 43$)	
Response	***n***	**%**	***n***	**%**	***n***	**%**
Complete response	2	7.4	0	0	2	4.7
Partial response	9	33.3	1	6.3	10	23.3
Stable disease	5	18.5	0	0	5	11.6
Progression	11	40.7	15	93.8	26	60.5
Objective response	11	40.7	1	6.3	12	27.9
Disease control	16	59.3	1	6.3	17	39.5

Abbreviation: CCRT, concurrent chemoradiotherapy.

Table 3. Phase II toxicity ($n = 43$)

	Grade 1/2		Grade 3/4	
Toxicity	***n***	**%**	***n***	**%**
Hematological events				
Anemia	10	23.3	26	60.5
Neutropenia	16	37.2	12	27.9
Thrombocytopenia	7	16.3	5	11.6
Febrile neutropenia	0	0.0	1	2.3
Nonhematological events				
Dysphagia	7	16.3	10	23.3
Anorexia	16	37.2	7	16.3
Dyspnea	12	27.9	6	14.0
Hoarseness	9	20.9	6	14.0
Hyponatremia	6	14.0	6	14.0
Nausea	20	46.5	7	16.3
Vomiting	17	39.5	7	16.3
Hypokalemia	0	0.0	5	11.6
Sore throat	14	32.6	5	11.6
Constipation	13	30.2	4	9.3
Cough	19	44.2	3	7.0
Fatigue	16	37.2	3	7.0
Insomnia	14	32.6	3	7.0
Hypercalcemia	1	2.3	2	4.7
Infection	7	16.3	2	4.7
Diarrhea	11	25.6	1	2.3
Fever	12	27.9	1	2.3

Table 4. Comparison of EORTC QLQ-C30 between the two study time points

QLQ-C30	At diagnosis	At 6th cycles	Difference (95% CI)	*p* value
Physical functioning[a]	44.3	52.3	8.0 (0.6 to 15.4)	.03
Role functioning[a]	43.9	58.9	15.0 (5.9 to 24.1)	<.01
Emotion functioning[a]	43.8	51.3	7.5 (1.3 to 13.7)	.02
Cognitive functioning	45.4	48.9	3.6 (−4.3 to 11.5)	.37
Social functioning	52.9	55.4	2.5 (−5.6 to 10.6)	.54
Global quality of life[b]	47.8	48.8	1.0 (−7.7 to 9.7)	.81
Fatigue	53.1	58.6	5.5 (−1.4 to 12.3)	.11
Nausea and vomiting[a]	34.3	48.9	14.6 (5.7 to 23.6)	<.01
Pain	57.5	59.3	1.8 (−6.3 to 9.9)	.66
Dyspnea	43.6	46.4	2.9 (−6.6 to 12.4)	.55
Insomnia	52.1	53.6	1.4 (−5.8 to 8.6)	.69
Loss of appetite	49.3	57.1	7.9 (−1.9 to 17.6)	.11
Constipation	48.6	50.0	1.4 (−7.1 to 10.0)	.74
Diarrhea[a]	32.1	45.0	12.9 (5.0 to 20.8)	<.01
Financial difficulties	53.6	54.3	0.7 (−7.5 to 8.9)	.86

[a] $p < .05$.
[b] A positive difference represents improvement.
Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire; CI, confidence interval.

Table 5. Comparison of QLQ-H&N35 scores between the two study time points

QLQ-H&N35	At diagnosis	At 6th cycles	Difference (95% CI)	*p* value
Pain	50.5	52.1	1.6 (−4.8 to 8.0)	.61
Swallowing	55.5	61.8	6.3 (−1.8 to 14.4)	.13
Senses	47.9	45.7	−2.1 (−9.4 to 5.1)	.55
Speech	57.1	59.1	1.9 (−1.8 to 14.4)	.64
Social eating	57.0	55.9	−1.1 (−8.3 to 6.1)	.76
Social contact	45.7	53.3	7.6 (0.7 to 14.5)	.03
Sexuality	57.9	60.0	2.1 (−5.3 to 9.6)	.56
Problems with teeth	57.9	59.3	1.4 (−7.1 to 10.0)	.74
Opening mouth wide	56.4	57.1	0.7 (−5.7 to 7.1)	.82
Dry mouth	61.4	58.6	−2.9 (−11.4 to 5.7)	.50
Sticky saliva	61.4	60.0	−1.5 (−10.7 to 7.9)	.76
Cough	58.6	60.0	1.5 (−6.9 to 9.7)	.73
Feeling ill	59.3	62.1	2.9 (−5.7 to 11.4)	.50
Painkillers	45.7	42.9	−2.9 (−6.3 to 0.6)	.10
Nutritional supplements	38.6	37.1	−1.4 (−7.3 to 4.4)	.62
Feeding tube	38.6	37.1	−1.4 (−6.1 to 3.2)	.54
Lost weight[a]	44.3	38.6	−5.7 (−11.3 to −0.2)	.04
Gained weight[b]	29.3	31.4	2.1 (−3.1 to 7.4)	.41

[a] $p < .05$.
[b] A positive difference represents an improvement.
Abbreviations: EORTC QLQ-H&N35, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire Head and Neck Cancer module; CI, confidence interval.