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

SAN-CHI CHEN, PETER MU-HSIN CHANG, MUH-HWA YANG

Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China; Faculty of Medicine and Institute of Clinical Medicine, National Yang Ming University, Taipei, Taiwan, Republic of China

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/m² 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/m² 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/m² 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...
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/m². Therefore, 60 mg/m² 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.

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 nonnasopharyngeal 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 g/dL, white blood cells <3,000 per mm³, absolute neutrophil count <1,500 per mm³, and platelets <100,000 per mm³); 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 (VGHTE-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/m² in 3 patient cohorts and then escalated with 5 mg/m² increments until a DLT occurred. Irinotecan was administered intravenously (i.v.) over 90 min on day 1, with cisplatin 50 mg/m² 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 $a$ and $b$ 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 $\geq 38.0^\circ C$ 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** | Irinotecan |
|------------|------------|
| **Generic/Working name** | Irinotecan |
| **Trade name** | Irino |
| **Company name** | TTY |
| **Drug type** | Topoisomerase I inhibitor |
| **Drug class** | Topoisomerase I |
| **Dose** | 60 mg/m² |
| **Route** | i.v. |

**Schedule of Administration**: Irinotecan was to be administered at doses of 40, 50, 60, and 70 mg/m² in each 3 patient step, and then escalated with 5 mg/m² 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** | Cisplatin |
|------------|-----------|
| **Generic/Working name** | Cisplatin |
| **Drug type** | Platinum compound |
| **Drug class** | Platinum compound |
| **Dose** | 50 mg/m² |
| **Route** | i.v. |

**Schedule of Administration**: Cisplatin was supplied with the dose of 50 mg/m² i.v. over 60 min on day 1 every 2 weeks a cycle.

| **Drug 3** | Tegafur/uracil |
|------------|---------------|
| **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

| Characteristic                  | Value                  |
|--------------------------------|------------------------|
| 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**

| Characteristic                  | Value                  |
|--------------------------------|------------------------|
| 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**

| Event                          | *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%         |
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/m² 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 chemoresistance 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.

**REFERENCES**

1. Vermorken JB, Mesia R, Rivera F et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–1127.
2. Kurzweg T, Möckelmann N, Laban E et al. Current treatment options for recurrent/metastatic head and neck cancer: A post-ASCO 2011 update and review of last year’s literature. Eur Arch Otorhinolaryngol 2012; 269:2157–2167.
3. Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695–1704.
4. Posner MR, Herschok DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–1715.
5. Janinis J, Papadakou M, Xidakis E et al. Combination chemotherapy with docetaxel, cisplatin, and 5-fluorouracil in previously treated patients with advanced/recurrent head and neck cancer: a phase II feasibility study. Am J Clin Oncol 2000;23:128–131.
6. Colevas AD, Amrein PC, Gomolin H et al. A phase II study of combined oral uracil and fluorouracil with leucovorin for patients with squamous cell carcinoma of the head and neck. Cancer 2001;92:326–331.
7. Xie R, Mathijssen RH, Sparreboom A et al. Clinical pharmacokinetics of irinotecan and its metabolites: A population analysis. J Clin Oncol 2002;20:3293–3301.
8. Gilbert J, Cmelak A, Shyr Y et al. Phase II trial of irinotecan plus cisplatin in patients with recurrent or metastatic squamous carcinoma of the head and neck. Cancer 2008;113:186–192.
9. Forastiere AA, Mutch B, Schuller DE et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Group study. J Clin Oncol 1992;10:1245–1251.
10. Jacobs C, Lyman G, Velez-Garcia E et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992;10:257–263.
11. Gibson MK, Li Y, Murphy B et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): An intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562–3567.
12. Iyer L, Das S, Janisch L et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics 2002;2:43–47.
13. Huang CS, Luo GA, Huang ML et al. Variations of the bilirubin uridine-diphosphoglucuronosyl transferase 1A1 gene in healthy Taiwanese. Pharmacogenetics 2000;10:539–544.
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

| Characteristic                      | Phase I (n = 14) | Phase II (n = 43) |
|-------------------------------------|------------------|-------------------|
|                                     | 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

| Response                  | No previous CCRT in < 6 m (n = 27) | Previous CCRT in < 6 m (n = 16) | All (n = 43) |
|---------------------------|------------------------------------|---------------------------------|--------------|
|                           | 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)

| Toxicity                | Grade 1/2 | Grade 3/4 |
|-------------------------|-----------|-----------|
|                         | 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.