Concurrent Chemoradiotherapy Using Cisplatin, Tegafur, and Leucovorin for Advanced Squamous Cell Carcinoma of the Hypopharynx and Oropharynx

Hung-Ming Wang[1], Cheng-Lung Hsu[1], Chia-Hsun Hsieh[1], Kang-Hsing Fan[2], Chien-Yu Lin[2], Joseph Tung-Chieh Chang[2], Shiang-Fu Huang[3], I-How Chen[3], Chun-Ta Liao[3], Shu-Kung Ng[4]

Background: To evaluate the efficacy and adverse events of cisplatin, tegafur, and leucovorin concomitantly with radiotherapy for patients with advanced, non-metastatic squamous cell carcinoma (SCC) of the oropharynx and hypopharynx.

Methods: The PTL regimen consisted of cisplatin (P) 50 mg/m^2 on day 1, oral tegafur (T) 800 mg/day plus leucovorin (LV) 60 mg/day on days 1 through 14. It was repeated every 2 weeks through the radiotherapy course. Conventional radiotherapy with 1.8-2.0 Gy/day, 5 days per week, was delivered in a total dose of between 70 and 72 Gy.

Results: Sixty-five patients with stage III or IV of SCC of the head and neck were consecutively treated between May 2002 and November 2005. Forty-six (70.7%) patients had complete response after concomitant chemoradiotherapy (CCRT). With a median follow-up of 54.0 months (range 1-103 months), the 5-year locoregional control, progression-free survival, and overall survival rates were 50.6%, 40.7%, and 59.7%, respectively. Three (4.6%) patients had toxic death during treatment. Fifty-one (80.0%) patients experienced grade 3-4 mucositis which occurred in about 35% of the CCRT duration. The functional preservation rate among post-CCRT complete responders was 93.5% (43/46). The median cisplatin accumulated dosage was 150 mg, and the rate of hearing impairment among the survivors was 7.8%.

Conclusion: CCRT with outpatient-based PTL for advanced SCC of oropharynx and hypopharynx is feasible and has comparative efficacy and acceptable adverse events.
(*Biomed J 2014;37:133-140*)

At a Glance Commentary

Scientific background of the subject

Updated meta-analysis shows that concomitant chemoradiotherapy (CCRT) is the standard treatment for SCCHN for intent of organ preservation and for unresectable diseases. However, studies investigated a variety of agents and schedule, and the optimum regimen is yet to be defined.

What this study adds to the field

The current study demonstrated that biweekly chemotherapy regimen of cisplatin/tegafur/leucovorin can be incorporated into radiotherapy for advanced sqaumous cell carcinoma of oropharynx and hypopharynx with comparative efficacy and acceptable adverse events.

Key words: chemoradiotherapy, chemotherapy, head and neck cancer, leucoverin, radiotherapy, tegafur

Combining chemotherapy and radiation therapy for patients with local advanced squamous cell carcinoma of the head and neck (SCCHN) has been extensively explored in the past decades. Several phase III trials and meta-analyses

From the [1]Division of Medical Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan; [2]Department of Radiation Oncology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan; [3]Section of Head and Neck Surgery, Department of Otorhinolaryngology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan; [4]Department of Diagnostic Radiology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan
Received: Mar. 23, 2013; Accepted: Jun. 19, 2013
Correspondence to: Dr. Hung-Ming Wang, Division of Medical Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou. 5 Fusing St., Gueishan, Taoyuan 333, Taiwan, (R.O.C.) Tel.: 886-3-3281200 ext. 8820; Fax: 886-3-3278211; E-mail: whm526@adm.cgmh.org.tw

DOI: 10.4103/2319-4170.117893

now allow us to make evidence-based recommendations that concomitant chemoradiotherapy (CCRT) may be the best way to incorporate chemotherapy into radiotherapy for treating patients with SCCHN.[1-6]

Cisplatin plus 5-flurouracil (5-FU) is still commonly used as induction chemotherapy or during CCRT for SCCHN.[7-10] The literature reports suggested that optimal scheduling of 5-FU as a radiosensitizer is strongly dependent on continuous exposure of tumor cells to 5-FU during irradiation for at least 8 hours.[11-13] Because of the short half-life of 5-FU, it must be administered as a continuous infusion to achieve prolonged tumor cell exposure at effective 5-FU levels. However, the continuous 5-FU infusion is limited in its need for an indwelling venous catheter and a portable infusion pump.

Eighty to ninety percent of SCCHN patients in Taiwan were betel quid chewers; 30-40% of them experienced mucositis World Health Organization (WHO) grade 3 from cisplatin/5-FU in a neoadjuvant chemotherapy setting. This was much higher than the 8-11% reported in Western populations and was related to oral submucous fibrosis from betel quid chewing.[14,15] To improve our patients' compliance to cisplatin/5-FU–based chemotherapy, we have demonstrated that outpatient-based cisplatin/oral 5-FU prodrugs/leucovorin (LV) combined regimens are of low toxicity and comparative efficacy to cisplatin/5-FU.[16,17] The oral 5-FU prodrugs also provide a substantial improvement in the ease of administration of 5-FU as a radiosensitizer. The aforementioned served as our rationale for using cisplatin/oral 5-FU prodrugs/LV for SCC of oropharynx and hypopharynx (SCCOH) treated primarily by CCRT. Here, we report our experience of routine practice using cisplatin/oral 5-FU prodrugs/LV in a prospectively assembled cohort comprising patients with SCCOH treated with CCRT between 2002 and 2005. This analysis was approved by institutional research ethics board.

METHODS

Eligibility criteria

The patients fulfilled the following criteria: Newly diagnosed, previously untreated SCCOH; stage III or IV disease; without distant metastasis; measurable disease documented by a computed tomography (CT) scan or magnetic resonance imaging (MRI); and a WHO performance status ≤ 2. They had an adequate bone marrow reserve (leukocyte count $\geq$ 4000/l and platelets $\geq$ 100,000/l), adequate renal function (serum creatinine < 2.0 mg/dl), and adequate liver function [total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) $\leq 2.5 \times$ ULN]. Patients with serious concomitant illness, for example, liver cirrhosis, angina, or myocardial disease, uncontrolled infection, or intestinal obstruction, malabsorption or any other condition that restricted the intake of oral medication, were ineligible. However, patients who were fed through nasogastric tubes or gastrostomy tubes without intestinal malabsorption or obstruction were eligible.

Pretreatment evaluation consisted of a history and physical examination, flexible fiber-optic equipment, measurement of all detectable tumors, chest X-rays, CT scan or MRI of the head and neck, bone scan, and liver echogram. Patients were staged in accordance with the 2002 American Joint Committee on Cancer staging system. All patients signed an informed consent before treatment.

Treatment plan

The chemotherapy regimen consisted of cisplatin (P) 50 mg/m^2 administered by continuous intravenous (IV) infusion for 3 h on day 1, oral tegafur (T) 800 mg/day on days 1 through 14, and oral leucovorin (L) 60 mg/day on days 1 through 14. This PTL regimen was delivered at outpatient clinics every 14 days. Tegafur was supplied as a 200-mg capsule and leucovorin as a 15-mg tablet. Both were administered concurrently in four dividing doses. Tegafur and leucovorin were powdered for tube-feeding patients. All patients received IV antiemetics of serotonin receptor (5-HT3) antagonists before cisplatin. Dexamethasone 2 mg daily for 7 days and metoclopramide 30 mg daily for 14 days were used to mitigate nausea and delayed emesis that would affect the compliance of oral medication. If there was $\geq$ grade 2 vomiting in the first cycle, oral 5-HT3 antagonists were prescribed for 5 more days after cisplatin in the next cycles. Compliance of oral tegafur was determined by patient reporting.

In all cases, radiotherapy was administered using 6-MV photon beams for 2 Gy per fraction, every fraction per day and 5 days a week. The radiotherapy area included gross tumor area with at least 1 cm margins and whole neck for 46 Gy, then cone-down boost to the initial gross tumor area with close margins to 72 Gy. Intensity-modulated radiotherapy (IMRT) was used in all patients.

Evaluation of adverse events and response

Adverse events were assessed according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0 and Radiation Therapy Oncology Group (RTOG) toxicity scoring system. Patients were assessed weekly for acute adverse events during CCRT. Tube feeding through nasogastric or percutaneous gastrostomic route was done as needed for ensuring adequate nutrition and compliance of oral medication.

For $\geq$ grade 2 neutropenia, thrombocytopenia, or liver dysfunction, the chemotherapy had to be withheld.

Chemotherapy was restarted without dose modification when the adverse event resolved to < grade 2. If febrile neurtopenia or thrombocytopenia with > 12 unit platelet transfusion was needed, the dose of tegafur was reduced by 200 mg/day when chemotherapy was restarted. Cisplatin was withheld when serum creatinine ≥ 2.0 mg/dl; patients were then treated with tegafur plus leucovorin only. For grade 4 radiation-related mucositis or dermatitis and grade 3 diarrhea, chemotherapy was withheld and restarted with a dose reduction of 200 mg tegafur per day when the adverse events resolved to ≤ grade 3 mucositis or dermatitis or ≤ grade 2 diarrhea. When a dose reduction was required, no dose re-escalation was performed subsequently. If >2 times of dose modifications were needed, the patient had to be taken off the study. Radiotherapy was withheld for grade 4 radiation-related mucositis or dermatitis, or uncontrolled infection. It was restarted when the adverse events resolved to ≤ grade 3 mucositis or dermatitis, and with no uncontrolled infection.

Response analysis was determined between 8 and 12 weeks after completion of definitive CCRT. A biopsy was performed if there were any clinical suspicions of a residual tumor. Patients were not routinely biopsied to confirm the absence of tumors. A complete response required the disappearance of all clinical, radiographic, and, if applicable, pathologic evidences of disease. Any pathologically confirmed residual disease would result in appropriate surgical resection. Neck dissection was not recommended for patients with N2-3 disease who achieved complete response after CCRT in both primary and neck lymph nodes. Salvage surgery was recommended, if appropriate, for local or regional disease recurrence.

Patients were followed up by the multidisciplinary team after completion of therapy every 2-3 months. Chest X-rays were obtained yearly, and other radiographic studies were performed as clinically indicated.

Statistical analysis

The time-to-event end points analyzed were overall survival (OS), progression-free survival (PFS), and locoregional control (LRC). The compliance to treatment, treatment-related adverse events, and the functional preservation status were also analyzed.

OS was defined as the time from treatment to death resulting from any cause. PFS was defined as the time from treatment until disease progression or relapse, or secondary primary, or death from any cause. LRC was defined as the time from treatment to failure of disease control above clavicle. Survival estimations were performed using the method of Kaplan–Meier. The logrank test was used for univariate analysis and the Cox proportional hazards model was used for multivariate analysis. All statistical computations were performed with the statistical software SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Between May 2002 and November 2005, a total of 65 consecutive patients who fulfilled the eligible criteria were recruited. The data were prospectively collected but retrospectively analyzed. The characteristics of the population are listed in Table 1, and the stages of tumor and lymph node are listed in Table 2. Stage III was found in 18 (26.2%) patients and stage IV in 47 (73.8%) patients.

Adverse events

The common acute adverse events are summarized in Table 3. The most common grade 3-4 adverse event was mucositis. Forty-seven patients (73.8%) experienced grade 3 mucositis and 4 (6.2%) patients experienced grade 4 mucositis. Two patients (3.1%) had grade 4 vomiting and 1 patient (1.5%) had grade 4 dermatitis. Grade 3-4 mucositis occurred in about 35% of the entire CCRT duration. Three patients (4.6%) died during CCRT as toxic death.

Table 1: Patient characteristics

Characteristics		Number (%)
Gender	Male/Female	63/2
Age	Median (range)	52 (37-76)
Performance status	0	30 (46.1)
	1	33 (50.8)
	2	2 (3.1)
Site	Oropharynx	35 (53.8)
	Tonsil	25 (38.5)
	Tongue base	9 (13.8)
	Soft palate	1 (1.5)
	Hypopharynx	30 (46.2)
Differentiation	Well	4 (6.2)
	Moderate	34 (52.3)
	Poor	11 (16.9)
	No description	16 (24.6)
Stage	III	17 (26.2)
	IVa	34 (52.3)
	IVb	14 (21.5)
Resectability	Resectable	48 (73.8)
	Unresectable	17 (26.2)

Table 2: Tumor–node staging

Tumor/node	0	1	2A	2B	2C	3	Total
1	0	0	1	1	0	1	3
2	0	3	3	3	0	1	10
3	10	5	2	2	3	0	22
4A	7	3	2	2	3	2	19
4B	1	2	0	2	4	2	11
Total	18	13	8	10	10	6	65

Stage III: 26.2%; stage IV: 73.8% (stage IVb: 21.5%)

Compliance

Thirty-one patients had received PTL chemotherapy before radiotherapy started. Twenty-two patients received one cycle, and nine patients received two cycles of PTL. One patient received only one cycle of chemotherapy and decided to undergo operation. The chemotherapy cycles delivered during the whole treatment course ranged from one to five, with a median of three cycles. Thirty patients (46.2%) received more than four cycles of PTL. The median cisplatin dosage was 75% (range 25-100%) of the scheduled dose and that of tegafur was 77.5% (range 17-100%). The median radiotherapy duration was 57 days (range 17-99 days) and median radiotherapy dosage was 7200 cGy (range 2400-7800 cGy). Five patients (7.7%) received a radiation dosage < 6000 cGy, which was given due to toxic death in three patients, intercurrent disease in one patient, and intolerance in one patient. Twenty-one patients needed hospitalization due to treatment-related side effects: infection in 12 patients, diarrhea in 1 patient, vomiting in 1 patient, and percutaneous gastrostomy feeding tube placement in 7 patients. Sixty-one patients (93.8%) experienced body weight loss, and 34 (52.3%) patients needed tube feeding during treatment. The compliance of treatment is summarized in Table 4.

Therapeutic results

The efficacy data were reported using the intent-to-treat patient population. After completion of CCRT with PTL regimen, 46 (70.7%) patients had complete response, 13 (20.0%) patients had partial response or stable disease, and 1 patient had progressive disease. Nine patients without complete response underwent operation for residual disease. Overall, 55 (84.6%) patients became disease-free after the CCRT with or without salvage surgery for residual disease.

The median follow-up period was 54.0 months (range 1-103 months). The 5-year LRC, PFS, and OS rates were 50.6%, 40.7%, and 59.7%, respectively [Figures 1-3]. The 5-year OS rates of post-CCRT complete responders and post-operation complete responders were 74.9% and 44.4%, respectively (logrank test $p = 0.019$). Of the 46 patients who had complete response after CCRT, 6 (13.0%) patients developed local recurrence, 2 (4.3%) patients had distant metastasis, 12 (26.1%) patients developed second primary cancer, 1 (2.1%) patient had local recurrence and second primary cancer, and 1 (2.1%) patient had distant metastasis and second primary cancer. Thirty-four patients (73.9%) were alive at the last follow-up (30 patients were cancer-free, 1 patient had hepatocellular carcinoma (HCC), and 3 patients had recurrent SCCHN). Of the nine patients who received an operation for post-CCRT residual disease, 4 (44.4%) experienced local recurrence, 1 (11.1%) developed second primary cancer, 1 (11.1%) had distant metastasis, and 3 (33.4%) patients were alive without disease. Totally, 33 (50.8%) patients were alive without disease, 1 (1.5%) patient was alive with HCC, and 4 (6.2%) patients had cancer recurrence, but were lost to follow-up. There were 27 (41.5%) patients who died either during or after treatment. Among these, 3 (4.6%) patients died during treatment, 2 (3.0%) patients died of intercurrent disease, 12 (18.4%) patients died of cancer recurrence or progression, and 10 (15.4%) patients died of second primary cancer.

The sites of 15 patients with second primary cancer were: Oral cavity 3, oropharynx 2 (1 patient had hypopharyngeal cancer first and developed tongue base cancer later and the other had left tonsil cancer first and developed right tonsil cancer 3 years later), hypopharynx 1 (this patient had tonsil cancer first), esophagus 3, lung 4, liver 1, and acute leukemia 1. The median time to develop second primary cancer was 36.0 months (range 5-62 months).

Regarding chronic adverse events, one patient who had received neck dissection had grade 3 neck fibrosis. Out of 46 post-CCRT complete responders, 2 patients had permanent tracheostomy (one due to adverse event of CCRT and the other one due to treatment for second primary) and

Table 3: Adverse events (according to NCI CTC version 2.0)

CTC grading Adverse event	% of CCRT duration					% of patients				
	0	1	2	3	4	0	1	2	3	4
Neutropenia	87.1	7.0	5.1	0.8		50.0	23.4	21.9	4.7	
Anemia	17.3	66.8	15.1	0.8		1.6	64.1	31.3	3.1	
Thrombocytopenia	72.8	24.9	2.3			42.2	45.3	12.5		
Vomiting	80.1	11.2	7.2	1.0	0.5	50.8	13.8	26.2	6.2	3.1
Mucositis	6.7	12.9	44.9	34.5	1.0	3.1	1.5	15.4	73.8	6.2
Dermatitis	24.3	38.9	33.4	3.0	0.4	7.7	15.4	66.2	9.2	1.5
Diarrhea	94.5	2.7	2.2	0.6		75.0	10.9	10.9	3.1	
Renal dysfunction	96.7	2.8	0.5			89.1	7.8	3.1		
Liver dysfunction	96.4	3.6				90.6	9.4			

Abbreviation: NCI CTC: National cancer institute, Common toxicity criteria

Table 4: Compliance to therapy

Chemotherapy administration	
Cycles [median (range)]	3 (1-5)
1/2/3/>=4	6.2/12.3/35.3/46.2 (%)
Dosage [median (range)]	
Cisplatin	75% (25-100%)
Oral 5-FU	77.5% (17-100%)
Body weight loss [mean (range)]	8.3% (1-23%)*
Hospitalization	21 (32.8%)†
Tube feeding	34 (53.1%)‡
Radiotherapy	
Duration [median (range)]	57 (17-99) days
Dosage<6000 cGy	5 patients

*: 61 patients (93.8%) had body weight loss; †: Causes of admission: infection 12, diarrhea 1, vomiting 1, for percutaneous gastrostomy creation 7; ‡: Percutaneous gastrostomy tube 24 (37.2%), nasogastric tube 10 (15.6%)

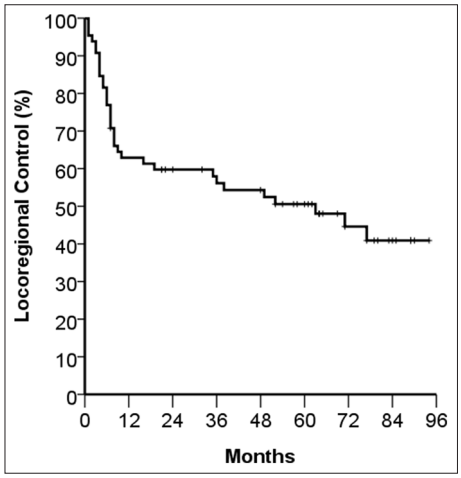

Figure 1: Locoregional control rate

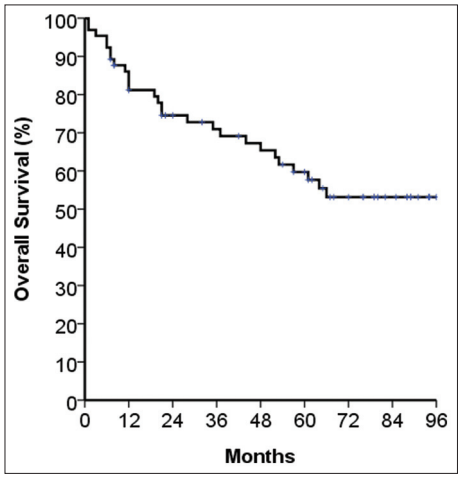

Figure 2: Progression-free survival rate

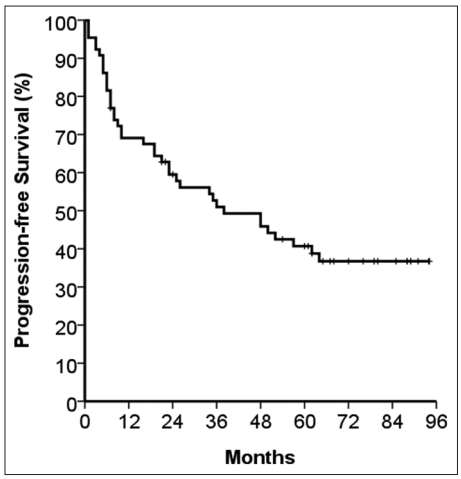

Figure 3: Overall survival rate

7 patients were on paste or liquid diet (3 were CCRT related, 2 due to operation for local recurrence, 1 due to treatment for second primary, and 1 due to stroke related dysphagia). The tracheostomy-free and tube-feeding free rate among post-CCRT complete responders was 93.5% (43/46). Three patients had strokes during follow-up. The ages of the patients who suffered strokes were 61, 68, and 74 years. The periods between completion of CCRT and occurrence of strokes were 12, 56, and 32 months, respectively. Additionally, there were 3 patients out of 38 (7.8%) who had hearing impairment that influenced their daily lives.

DISCUSSION

According to the large meta-analyses conducted based on individual patient data of randomized trials, CCRT is the standard treatment for locally advanced SCCHN.[5,18] CCRT conferred an absolute survival benefit of 8.6% at 5 years for cancer-related death. The survival benefit mostly comes from decreasing local failure (9.3% at 5 years) rather than distant failure (2.5% at 5 years). Regarding the optimal chemotherapy regimen, according to the meta-analyses, cisplatin alone, or cisplatin or carboplatin associated with 5-FU provided similar benefit.[18]

The optimal dose of cisplatin administration during CCRT is still controversial. Many studies use cisplatin 100 mg/m^2 bolus dosing on days 1, 22, and 43 of radiotherapy. However, compliance is a problem with the three-cycle high-dose cisplatin. Nearly one-third of patients do not complete all cycles, and subset analyses suggested that two cycles with a total of 200 mg/m^2 cisplatin are as effective as three cycles.[1,3,4] Lower doses of CDDP, for example, 30-40 mg/m^2 weekly, are also commonly used. However, there is no direct comparison between weekly low-dose CDDP and 3-week high-dose CDDP. Our PTL regimen used cisplatin 50 mg/m^2 biweekly with a plan to administer 200 mg/m^2 cisplatin during CCRT, and achieved a median dosage of received was 150 mg/m^2.

The complete response rate of primary CCRT in our study was 70.7%. The 5-year LRC, PFS, and OS rates of our study were 50.6%, 40.7%, and 59.7%, respectively. The reported 5-year LRC and OS rates in studies using comparable CCRT, as reported in the literature, range from 47 to 77% and from 22 to 50%, respectively.[2,19-23] In the updated analyses of Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC),[18] the 5-year overall survival for CCRT was 33.7%, with an absolute benefit of 6.5% at 5 years than just RT alone. The lower-dose CDDP regimen we used could achieve comparable results to those obtained with a higher cisplatin dose.

Our report included patients of SCCHN arising from oropharynx and hypopharynx, and their 5-year overall survival was 53% for oropharynx and 67% for hypopharynx (p = 0.681). The median survival was 65.6 months (95% confidence interval, 51.3-80.0 months) and 65.9 months (95% confidence interval, 53.3-78.5 months) for oropharynx and hypopharynx, respectively. In Taiwan,

Table 5: Trials of concurrent chemoradiotherapy with platinum plus oral 5-FU prodrugs for head and neck cancer

Authors	*N*	Radiotherapy, Gy	Chemotherapy	Complete response, %	Locoregional control	Overall survival	≥Gr 3 mucositis, %
Segura, 2005	58	65-70	Carboplatin 100 mg/m^2/week UFT 400 mg/day	41.0	10 months (median)	18.4 months (median)	47.0
Kim, 2005	37	70-70.2	Cisplatin 80 mg/m^2 on day 1, capecitabine 825 mg/m^2 bid on day 1-14; every 3 weeks a cycle, for two cycles	78.4	72.6% (2-year)	76.8% (2-year)	67.6
Fesneau, 2010	72	70	Carboplatin 70 mg/m^2/day on day 1-4, every 21 days a cycle, for three cycles; UFT 300 mg/m^2/day+LV 75 mg/day on day 1-19, day 29-47	NA	33.1% (3-year)	41.9% (3-year)	62.0
Wang, 2013	65	70-72	Cisplatin 50 mg/m^2 on day 1, Tegafur 800 mg/day+LV 60 mg/day on day 1-14; every 2 weeks a cycle, for four cycles	70.7	50.6% (5-year)	59.7% (5-year)	80.0

Abbreviation: NA: Not available

for patients treated between 2004 and 2010, the 5-year OS of stage III and IV oropharyngeal cancer was 43.1% and 30.8%, respectively, and those of hypopharyngeal cancer was 36.7% and 22.5%, respectively.[24]

Patients with SCCHN are at high risk of death resulting from noncancer causes and second primary cancer (i.e. competing mortality).[25,26] In our study, second primary cancer developed in 14 of 46 post-CCRT complete responders and 1 of 9 post-CCRT/surgery complete responders. It accounts for 37% (10/27) of all-cause mortality. The high incidences of competing events degrade the efficiency of clinical studies. Risk stratification of patients for competing mortality may lead to more efficient and clinically appropriate designs for future study.[26]

Radiation-induced sensorineural hearing loss and CDDP-induced ototoxicity are well-known adverse events. Concurrent CDDP with radiotherapy resulted in comparatively worse sensorineural hearing than just radiotherapy alone.[27,28] This risk did not seem to depend on cumulative doses of cisplatin, but on the fractional dose used per cycle.[29] According to a report by Zuur,[30] grade 3 hearing impairment (CTCAEv3.0) was 5% in low-dose cisplatin (6 mg/m^2/day for 20-25 days) and 32% in high-dose cisplatin (100 mg/m^2 for three infusions). In a prospective study by Hitchcock,[29] patients who received high-dose cisplatin also had more risk of hearing loss than those who received a low dose. In our study, the hearing impairment rate among the survivors was 7.8%. The lower cisplatin dose might translate to lower incidence of hearing impairment.

Byfield demonstrated that the sensitizing effects of 5-FU *in vitro* are maximal when exposure to 5-FU occurs for at least 24 h and up to 48 h after radiation exposure.[12] This supports the continuous infusion approach (i.e., 1000 mg/m^2/day for 5 days) when given with fractionated irradiation.[31,32] Tegafur, UFT (tegafur + uracil), S-1 (tegafur + gimeracil + oxonic acid), and capecitabine are the currently available oral 5-FU prodrugs.[33] They all have radiosensitization and different toxicity profiles. Table 5 lists the phase II trial of CCRT using platinum and oral 5-FU for SCCHN.[21-23] PTL has comparable effects to the other oral 5-FU regimens. Eighty percent of our patients experienced grade 3-4 mucositis, and they suffered from severe toxicity for only about 35% of the CCRT duration. The higher incidence of severe mucositis in our patients may be due to betel quid chewing–related chronic mucosa damage.[18] Though there was a higher incidence of grade 3-4 mucositis, only five patients received RT dose < 6000 Gy. The median administered CDDP dose was 75% of the scheduled dosage and that of tegafur was 77.5%. The compliance was not different from that reported in the other oral 5-FU trials.

Conclusion

CCRT is the standard treatment for SCCHN, when organ preservation is desired or for unresectable diseases. During 2002-2005, 65 patients with advanced stage III or IV SCCHN in our hospital received CCRT with PTL regimen. After 5 years of follow-up, these patients had comparable LRC and OS, with good functional preservation rates. PTL could be one option of CCRT for SCCHN. However, further studies are still necessary to confirm the benefit.

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