Phase II trial of cisplatin, tegafur plus uracil and leucovorin as neoadjuvant chemotherapy in patients with squamous cell carcinoma of the oropharynx and hypopharynx

Hung-Ming Wang[a], Chung-Tsen Hsueh[b], Cheng-Su Wang[a], I-How Chen[c], Chun-Ta Liao[c], Ming-Hsui Tsai[d], Shih-Peng Yeh[b] and Joseph Tung-Chieh Chang[e]

We evaluated the efficacy and toxicity of cisplatin, tegafur plus uracil and leucovorin as neoadjuvant chemotherapy for locally advanced squamous cell carcinoma (SCC) of the oropharynx and hypopharynx. Forty-six patients (stage IV, 83%; N2/3, 52%) were treated with PUL (50 mg/m^2 cisplatin on day 1, 300 mg/m^2 tegafur plus uracil orally and 60 mg leucovorin orally on days 1–14) over a 14-day cycle. Evaluation after 3 cycles led to chemotherapy termination if primary tumor responses were less than partial responses. Otherwise, PUL was continued up to 6 cycles before locoregional therapy. Patients achieving at least good partial responses at the primary site after neoadjuvant chemotherapy received radiotherapy for organ preservation. Chemotherapy responses were analyzed by intent-to-treat. Response rates of primary sites were 71.7% (33 of 46) with 34.8% (16 of 46) showing a complete response. Thirty patients (65.2%) achieved good partial responses at the primary site. Overall response and complete response rates of neck lymph nodes were 68.6% (24 of 35) and 25.7% (nine of 35). The combined response rate of primary site and neck lymph nodes was 63% (95% confidence interval 48.5–77.5%) with a complete response rate of 15.2%. Toxicities of WHO grade 3–4 included anemia (19.6%), diarrhea (17.4%) and neutropenia (8.7%). With a median follow-up of 36 months, overall survival and disease-free survival rates were 45.7% (21 of 46) and 41.3% (19 of 46); organ preservation rate was 90% (19 of 21). We concluded that the outpatient PUL regimen was a moderately effective, less-toxic neoadjuvant chemotherapy for SCC of the oropharynx and hypopharynx. PUL should be studied further with other active agents or radiotherapy. *Anti-Cancer Drugs* 16:447–453 © 2005 Lippincott Williams & Wilkins.

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[a]Division of Hematology/Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Taipei, Taiwan, [b]Division of Hematology/Oncology, Department of Internal Medicine, China Medical College Hospital, Taichung, Taiwan, [c]Department of Otolaryngology Head and Neck Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan, [d]Department of Otolaryngology Head and Neck Surgery, China Medical College Hospital, Taichung, Taiwan and [e]Department of Radiotherapy, Chang Gung Memorial Hospital, Taipei, Taiwan.

Correspondence to H.-M. Wang, Division of Hematology/Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, 199, Tun Hwa North Road, Taipei 105, Taiwan.
Tel: +886 3 3281200 extn 2114; fax: +886 3 3278211;
e-mail: whm526@ms12.hinet.net

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Introduction

Cisplatin plus 5-fluorouracil (5-FU) is the most common chemotherapy used for patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [1,2]. Its response rate for treatment-naive patients with locally advanced disease varies between 75 and 85%. A complete response was seen in 25–35%, and the complete response rate at the primary site was between 35 and 55% [1–5]. At present, there is enough evidence to support the view that larynx preservation is feasible if neoadjuvant chemotherapy of cisplatin/5-FU is followed by radiotherapy in patients with laryngeal and hypopharyngeal SCCHN [3,4]. Cisplatin/5-FU has also been shown to increase survival and disease-free survival in patients with unresectable disease when given definite radiotherapy [5].

SCCHN is the second most common cancer occurring in male Taiwanese individuals aged between 30 and 59 years old [6]. Of our SCCHN patients, 80–90% were betel quid chewers. About one-third of them were found to have betel quid-related oral submucous fibrosis (OSF). Patients with OSF were more susceptible to cisplatin/5-FU-related mucositis [7]. Of our patients, 30–40% experienced mucositis from cisplatin/5-FU that was greater than WHO grade 3. This required a reduced dose intensity and resulted in an unsatisfactory response rate [8]. Hospitalization for cisplatin/5-FU because of the need of hydration for cisplatin and emesis were other sources of stress and discomfort. These concerns motivated us to try to improve the efficacy and toxicity profiles of chemotherapy for our patients with SCCHN.

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Tegafur plus uracil (UFT) is a combination of tegafur and uracil in a 1:4 molar ratio. Uracil competitively inhibits the degradation of 5-FU by dihydropyrimidine dehydrogenase, which thus increases the amount of 5-FU available for cytotoxicity. Clinical studies using UFT in head and neck tumors demonstrated a 6.3 times greater concentration of 5-FU in tumor tissue than in non-tumoral tissue [9,10]. Chemosensitivity assays showed that UFT was the most effective of the 5-FU analogs against SCCHN [11]. UFT activity in head and neck cancer has been reported in the range of 24–30% by Japanese researchers [12,13] and cisplatin/UFT was shown to be as effective as the cisplatin/5-FU [14].

The literature shows that others have tried to improve the response rate to cisplatin/5-FU by adding folinic acid to biomodulate the 5-FU effect on thymidylate synthetase. Induction chemotherapy trials of cisplatin, 5-FU and high-dose i.v. leucovorin for SCCHN had a 80–90% response rate and a 50–69% complete response rate at the primary tumor site [15,16]. However, the toxicities, especially stomatitis and leukopenia, increased substantially. In contrast to i.v. leucovorin, oral leucovorin has been shown to result in low ratios of *d*/*l*-reduced folates, which may be important in maximizing the effectiveness of 5-FU/leucovorin [17]. *In vitro* studies have demonstrated that enhancement of the cytotoxic activity of UFT can be observed after 96-h exposure to oral *l*-leucovorin [18], and combined treatment using UFT with oral *l*-leucovorin was the most effective of various 5-FU derivatives [19]. A phase I trial of UFT plus oral leucovorin showed a favorable toxicity profile compared with that of i.v. regimens of 5-FU plus leucovorin [20]. The recommended phase II UFT trial starting dose is 300 mg/m^2/day plus 150 mg/day leucovorin [20]. In SCCHN, UFT 300 mg/m^2/day with oral leucovorin 90 mg/day achieved a 21% response rate in a phase II study [21].

We designed this phase II trial to evaluate the response and toxicity profile of outpatient chemotherapy using cisplatin, UFUR (a genuine tegafur plus uracil produced by Taiwan Tung Yang Biopharm) and leucovorin as an outpatient neoadjuvant chemotherapy for patients with SCCHN.

Methods

Patients with histologically confirmed squamous cell carcinoma of the hypopharynx or oropharynx were eligible for this study. They were also required to have resectable stage III or IV disease without distant metastases according to the staging system of the American Joint Committee on Cancer 1997 [22], to have had no previous treatment, to be < 70 years old, to have a performance status (PS) of ≤ 2 on the WHO scale, and to have adequate bone marrow function (leukocyte count $\geq 4000/\mu l$ and platelets $\geq 100\,000/\mu l$), adequate renal function (serum creatinine ≤ 1.4 mg/dl) and adequate liver function [total bilirubin $\leq 1.5\times$ upper limit of normal (ULN), sGOT and sGPT $\leq 2.5\times$ ULN]. Patients who had serious concomitant illnesses, e.g. liver cirrhosis, angina or myocardial disease, or had intestinal obstruction, malabsorption or any other condition preventing their taking oral medication, were ineligible. However, patients fed with a nasogastric tube, but without intestinal malabsorption or obstruction, were eligible. Patients with previous or concurrent malignancy were excluded.

All patients were initially evaluated by a multidisciplinary team. The evaluation included a medical history, clinical examination, flexible fiber optic nasopharyngoscopy with photographic recording, complete blood cell count, complete blood chemistry, head and neck computed tomographic (CT) scan or magnetic resonance imaging (MRI), chest X-ray, bone scan, and liver echography. The study design was reviewed and approved by the investigational review boards of the participating institutions and National Institutes of Health, and informed consent was obtained from patients.

The chemotherapy regimen of PUL consisted of cisplatin 50 mg/m^2 administered by continuous i.v. infusion for 3 h on day 1, oral UFUR 300 mg/m^2/day on day 1–14 and oral leucovorin 60 mg/day on day 1–14. All drugs were delivered at outpatient clinics and each cycle was repeated every 14 days. Cisplatin 50 mg/m^2 was administered in 500 ml of 0.9% normal saline (NS) or 5% dextrose 0.9% normal saline (D5S) infused over 3 h. Mannitol 30 g was added to the cisplatin solution to ensure an adequate urine output. A serotonin receptor antagonist was used as an antiemetic before cisplatin. Dexamethasone 2 mg daily for 7 days and metoclopramide 30 mg daily for 14 days were used to minimize the nausea or delayed emesis. If there was greater than grade 2 vomiting in the previous cycle, oral anti-serotonin was prescribed for 5 days after cisplatin in subsequent cycles. UFUR was supplied as 100-mg capsules and the calculated dose was rounded to the nearest 100 mg. The total daily dose was divided into three doses administered orally every 8 h (at approximately 7 a.m., 3 p.m. and 11 p.m.). If the capsule dose could not be divided equally, the highest dose was administered in the morning and the lower dose in the evening. Leucovorin was supplied as 15-mg tablets and administered concurrently with UFUR. The first leucovorin dose (at 7 a.m.) was 30 mg, and the 3 p.m. and 11 p.m. doses were each 15 mg. Patients were advised to consume no food 1 h before and after ingestion of the medication.

Dose-modification criteria were designed to reduce the dose of UFUR. The dose of leucovorin remained at

60 mg/day. Toxicities to chemotherapy were quantified using the WHO criteria and were evaluated once per cycle on the 14th day. For those patients with neutrophils $< 1500/mm^3$ or platelets $< 1 \times 10^5/mm^3$, treatment was postponed for a maximum of 2 weeks. After that time, if the neutrophil count was $1–1.5 \times 10^3/mm^3$ or the platelet count was $0.7–1 \times 10^5/mm^3$, then the dose of UFUR was reduced by $50\,mg/m^2$/day, and if lower neutrophil or platelet values resulted, chemotherapy was discontinued. If a patient had non-hematological toxicity at a grade ≥ 3, the patient would have had to recover completely within a maximum of 4 weeks and the daily dose of UFUR was reduced by $50\,mg/m^2$ on subsequent courses. If treatment could not be restarted on day 29, patients were taken off the study. Patient's compliance with UFUR was verified by counting the remaining pills at the end of each treatment course.

Responses were evaluated based on the WHO criteria, and quantified by physical examination, flexible fiber optic equipment and CT scan or MRI. Complete response was defined as disappearance of all clinically evident tumors. Good partial response was defined as a greater than 75% reduction in the product of the two largest perpendicular diameters of all measurable disease. Partial response was defined as a greater than 50% reduction in the product of the two largest perpendicular diameters of all measurable disease. No response was defined as any response less than partial response, stable disease or progression of disease, or death while on chemotherapy. Responses at the primary site and the regional nodes were scored separately, and the overall response was based on the worst of the two responses.

The PUL was administered at outpatient clinics for a 14-day cycle. A maximum of 6 cycles were given before locoregional therapy. Patients were considered assessable for responses if they received a minimum of 3 cycles of PUL with at least one follow-up assessment that was assessable for response. Initial evaluation after 3 cycles of PUL led to the termination of chemotherapy if the response at the primary site was less than a partial response. For complete or partial responders at the primary site and without progressive disease at lymph nodes, a further 3 cycles of chemotherapy were given before local therapy. PUL was immediately discontinued upon evidence of tumor progression or excessive toxicity.

Patients whose primary tumor failed to achieve at least a partial response after 3 cycles of chemotherapy or a good partial response after 6 cycles of chemotherapy had to undergo surgery followed by radiotherapy or concurrent chemoradiotherapy. Patients who achieved a good partial response or complete response at the primary sites received radiotherapy or concurrent chemoradiotherapy for organ preservation, and surgery was reserved for residual or recurrent disease after radiotherapy. In patients who achieved a good partial response or complete response at the primary tumor site after chemotherapy, but failed to achieve partial response for their neck disease, neck dissection was recommended before radiotherapy. Post-radiation neck dissection was carried out in all patients who failed to achieve a clinical complete response in the neck 6–8 weeks after completion of radiotherapy.

Megavoltage radiotherapy was administered using conventional fractionation (one fraction of 1.8–2 Gy, 5 days a week). In the case of definite radiotherapy delivered after chemotherapy, a dose of 46–46.8 Gy was given, followed by a booster dose of 24–26 Gy, at the tumor site and palpable lymph nodes, if present. When delivered post-operatively, the dose was 46–46.8 Gy followed by a booster dose of 20–24 Gy. The chemotherapy regimen for concurrent chemoradiotherapy was not specified in the design of the trial.

The primary efficacy endpoints were response rates and toxicity profiles. Point estimates and 95% confidence intervals for response rates will be obtained for intent-to-treat populations. Descriptive statistics were summarized using frequencies, percentages, means, SDs and ranges. Survival curves were estimated using the Kaplan–Meier technique. This study was designed to have a type I error of 5% to detect an expected response rate of approximately 70%. Forty-two evaluable patients would have needed to be enrolled to claim that the difference between the estimated and true proportion will be within $\pm 14\%$. With an estimated non-evaluable rate of 10%, 46 patients needed to be accrued in this study.

Results

From August 1999 to July 2001, 46 patients were consecutively enrolled. The characteristics of this cohort are listed in Table 1 and the tumor node staging is listed in Table 2. We observed stage III in eight patients (17%), stage IV in 38 patients (83%), T4 in 28 patients (61%), and N2/3 in 24 patients (52%).

We administered 230 cycles of PUL to 46 patients, with a median of 6 cycles (range 2–6 cycles) per patient. The

Table 1 Patient characteristics

Gender (male:female)	45:1
Age [median (range)]	48 (34–67)
Primary tumor site	
tongue base	7
tonsil	11
soft palate	1
hypopharynx	27
Performance status	
0	34
1	11
2	1

reasons for early discontinuance of PUL were: diarrhea, $n = 3$; prolonged myelosuppression, $n = 5$; cerebral vascular accident, $n = 1$; renal insufficiency, $n = 1$; and refusal of therapy, $n = 2$. One patient refused further therapy after his third cycle of chemotherapy and he did not bring back the residual UFUR tablets for pill counting. The compliance of the remaining 45 patients was $88.3 \pm 8.4\%$.

Non-hematologic toxicities were assessable in 230 cycles and hematologic toxicities in 229 cycles (see Table 3). The most common toxicities grade ≥ 3 were (% of patients): anemia 19.6%, diarrhea 17.4% and neutropenia 8.7%. Thirty-four (73.9%) patients had their nadir of hemoglobin < 11.0 mg/dl (grade > 1) and 59% of them showed macrocytic anemia. The mean value of mean corpuscular volume (MCV) changed from 94.1 ± 6.9 to $100.2 \pm 8.1\,\mu m^3$, which was accompanied by anemia grade ≥ 3 (Hb < 8.0 mg/dl) in 19.6% of patients. Blood transfusions were needed in 11 (24%) patients for symptomatic anemia.

Diarrhea of degree grade ≥ 2 occurred in 8.2% of cycles and 28.3% of patients. Fifty-eight percent of the instances of diarrhea occurred within the second and fourth cycle of chemotherapy, and the diarrhea usually remitted shortly after stopping the UFUR at the beginning of the diarrhea. Hospitalization was needed in 3 cycles in three different patients due to diarrhea associated with a moderate degree of infection. Neutropenia grade ≥ 3 occurred in 3.2% of cycles and 14.3% of patients. Only one episode of neutropenic fever (without life-threatening sepsis) occurred.

One patient was withdrawn from chemotherapy on his third cycle because of grade 4 ($> 10 \times$ UNL) elevation of liver function and no response of his tumor. He died of pneumonia 1.5 months after withdrawing from the trial. Skin manifestations included skin rash in three patients, pruritis in two and pigmentation in three. No hand–foot syndrome was observed. Epigastric discomfort requiring medical management occurred in 19 cycles within 12 patients.

Of 46 patients, 43 were assessable for response. One patient refused further therapy after his third cycle of chemotherapy because of back pain that he mistook for renal damage from chemotherapy. One patient had a cerebral vascular accident 2 days after starting his third cycle of chemotherapy and was withdrawn from the trial. One patient experienced renal insufficiency after his second cycle of chemotherapy and was then removed from the study. All three of these patients were not adequately reassessed for response and were included in the analysis as non-responders. At the primary tumor site, 16 of 46 patients (34.8%) achieved a complete response and 17 patients achieved a partial response, for an overall response rate of 71.7% (33/46). Thirty patients (65.2%) achieved good partial response at the primary site and received radiotherapy or chemoradiotherapy as the schema for organ sparing. In 35 patients with neck lymph nodes metastases, nine patients (25.7%) achieved a complete response and 15 patients (42.9%) achieved a partial response. On an intent-to-treat analysis, the combined primary tumor site and lymph node response was 15.2% (seven of 46) complete response and the overall response rate was 63% (29 of 46) (95% confidence interval 48.5–77.5%). With a median follow-up of 36

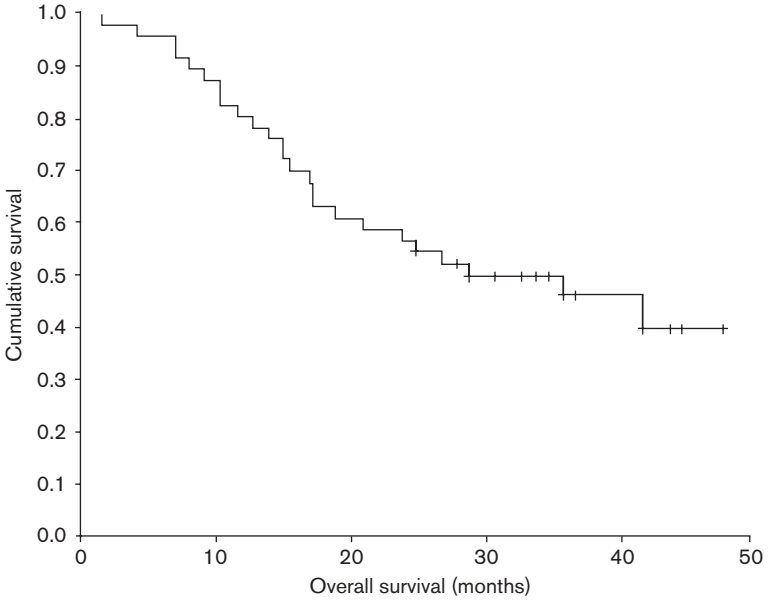
Table 2 Tumor node staging

Tumor/node	0	1	2A	2B	2C	3	Total
1		1				1	2
2		2		3		1	6
3	3	2	2	3			10
4	8	6	1	8	4	1	28
Total	11	11	3	14	4	3	46

Table 3 Toxicity (by WHO grading)

	Percent of cycles					Percent of patients				
	0	1	2	3	4	0	1	2	3	4
Leukocyte	83.9	9.6	4.3	2.2		56.5	21.7	13.0	8.7	
Neutrophil	86.1	7.0	4.8	2.2		54.3	17.4	19.6	8.7	
Platelet	95.2	2.6	2.2			78.3	13.0	8.7		
Anemia	47.8	27.0	18.3	6.5	0.4	28.3	19.6	32.6	17.4	2.2
Vomiting	79.1	13.0	7.0	0.4	0.4	45.7	30.4	19.6	2.2	2.2
Mucosa	85.2	7.0	7.0	0.8		63.0	13.0	19.6	4.3	
Diarrhea	83.5	8.3	3.9	3.9	0.4	47.8	23.9	10.9	15.2	2.2
Renal	97.8	1.7	0.4			91.3	6.5	2.2		
Hepatic	91.3	7.0	0.4	0.9	0.4	73.9	19.6	2.2	2.2	2.2
Infection	96.1	3.9				84.8	15.2			
Allergy	100.0					100.0				
Alopecia	89.6	10.4				91.3	8.7			
Skin	94.8	2.2	3.0			89.1	4.3	6.5		
Hand–foot syndrome	100.0					100.0				
Neurologic	93.6	5.7	0.7			71.7	26.1	2.2		
Pulmonary	99.6	0.4				97.8	2.2			

Fig. 1



Kaplan–Meier curve of overall survival for 46 patients.

months (range 25–48 months), the overall survival and disease-free survival rate of the entire group of 46 patients was 45.7% (21 of 46) (Fig. 1) and 41.3% (19 of 46), respectively. Organ preservation was achieved in 90% (19 of 21) of the surviving patients.

Discussion

This phase II trial using cisplatin, UFUR and leucovorin in advanced SCC of oropharynx and hypopharynx demonstrated that it is generally well tolerated. The most common toxicities were diarrhea and anemia. Diarrhea is typical of low-dose, continuous, fluoropyrimidine-based therapy and is expected for oral UFUR, the side-effects of which mimic those of protracted, low-dose 5-FU therapy [23]. A 17.4% incidence of diarrhea grade ≥ 3 was comparable to rates in the literature where UFT/leucovorin was used [21]. Mucositis was a minor distress in this study.

The frequency and magnitude of anemia in this trial were not observed in previous studies that used cisplatin/UFT [14] or UFT/leucovorin in SCCHN [21]. These studies reported no anemia grade ≥ 3, and that the incidence of anemia of grade 2 was 5.9 and 17% of patients, respectively. Since macrocytic anemia had also been documented in previous studies of prolonged use of concurrent infusion of 5-FU plus leucovorin and weekly bolus cisplatin in metastatic colorectal cancer [24], we think that the protracted use of UFUR plus leucovorin concurrently with cisplatin could produce persistent inhibition of thymidylate synthesis and DNA-directed toxicity to produce macrocytic anemia. Study of bone marrow with macrocytic erythropoiesis from continuous 5-FU exposure had shown that the recovery of marrow to normoblastic hematopoiesis was apparent within 3–5 days after discontinuing 5-FU [25]. These findings may explain why macrocytic anemia was not so prominent in the literature studies of SCCHN using cisplatin/UFT or UFT/leucovorin and with a 7-day treatment-free period between each cycle [14,21]. Therefore, the therapeutic schema of PUL in future applications of this low-toxicity regimen in relatively long-term palliative use may need modification.

Patients' compliance to oral chemotherapy has serious implications for treatment. In this report, compliance as measured by pill count was $88.3 \pm 8.4\%$. Beside the patient's motivation, another factor affecting compliance was side-effects, especially emesis. Cisplatin is a strong emetic agent and delayed emesis may have serious implications for oral chemotherapy compliance. The prophylactic antiemetic schema used in this report seems acceptable with emesis of grade 2 or higher in only 7.8% of all cycles. Reduced compliance by patients because of discomfort, e.g. leukopenia-related fatigue or diarrhea, may protect them from worse conditions. Oral compliance should be monitored and judged carefully, and patients should not be asked inappropriately to strictly adhere to their medication schedule.

The overall response rate of 68% with a complete response of 17% in this report was not as good as rates

achieved by cisplatin/5-FU in randomized phase III trials of organ preservation [3–5]. Nonetheless, our study enrolled a higher proportion of patients with tumor class T4 (61%) and/or stage IV (83%) than in the randomized trials (T4, 4–26%; stage IV, 34–44%) [3,4]. This may account for the lower response rate seen in our study. Compared to our previous studies of 103 SCCHN patients with tumors arising from the hypopharynx and oropharynx with similar tumor extents treated using the cisplatin/5-FU-based regimen (response rate of 51% with a CR of 11% and 37% grade ≥ 3 mucositis) [7,8], the present study showed PUL had even better activity. Furthermore, there was a substantial reduction in toxicity, especially in mucositis.

Literature reports have documented that cisplatin/5-FU is an effective replacement for surgery in organ-sparing therapy for patients with laryngeal or hypopharyngeal SCCHN [3,4], and this approach is also feasible and worthy of further testing in oropharyngeal cancer [26–28]. Since SCCHN patients receiving pre-operative UFT had a high tissue concentration of 5-FU in the tongue, hypopharynx and mesopharynx [10], and the difference in the 5-FU concentration between the tumor and normal tissues was larger in pharyngeal cancer [10], UFT has a potential role in organ-sparing therapy for SCCHN of the pharynx. The 65% good partial response with a 35% complete response at the primary tumor rendered organ-sparing therapy (as per our schema) feasible in most of our patients. Locoregional therapies after the neoadjuvant chemotherapy is still the major determinant of patients' survival. Randomized trials and meta-analysis have both demonstrated a survival benefit with concurrent chemoradiotherapy in combined approaches for SCCHN [29,30], and neoadjuvant chemotherapy followed by concurrent chemoradiotherapy has been advocated in the literature [31]. Although cisplatin-based concurrent chemoradiotherapy for locoregional therapies was used in the majority of our patients, it was not specified in the design of the trial and it was difficult to assess impact of cisplatin-based concurrent chemoradiotherapy on the overall outcome. The 3-year 46% overall survival (Fig. 1) and 44% disease-free survival in our patients (most of whom had advanced or hypopharyngeal cancer) were comparable to those in previous studies using induction chemotherapy of cisplatin/5-FU followed by radiotherapy or conventional therapy for SCC of the hypopharynx [4,32]. Organ preservation was achieved in 90% (19 of 21) of our surviving patients. These results suggest that using PUL as a neoadjuvant chemotherapy for organ preservation is feasible.

In conclusion, the PUL regimen provided a comparative efficacy and better toxicity profile to the cisplatin/5-FU regimen in our patients. Because it can be used at outpatient clinics, it may reduce the adverse impact of chemotherapy on the patients' quality of life and socioeconomic status. The low hematologic toxicity of PUL may warrant application of this regimen in combination with taxenes which are effective in SCCHN, but cause a substantial amount of neutropenia and mucositis [33,34]. The advantage of outpatient chemotherapy and minor degree of mucositis of PUL also warrants its application in concurrent chemoradiotherapy for SCCHN.

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