Cisplatin, Tegafur, and Leucovorin

A Moderately Effective and Minimally Toxic Outpatient Neoadjuvant Chemotherapy for Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Hung-Ming Wang, M.D.[1]
Cheng-Su Wang, M.D.[1]
Jen-Shi Chen, M.D.[1]
I-How Chen, M.D.[2]
Chun-Ta Liao, M.D.[2]
Tung-Chieh Joseph Chang, M.D.[3]

[1] Division of Hematology/Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Taipei, Taiwan, Republic of China.

[2] Department of Otolaryngology Head and Neck Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan, Republic of China.

[3] Department of Radiotherapy, Chang Gung Memorial Hospital, Taipei, Taiwan, Republic of China.

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Address for reprints: Hung-Ming Wang, M.D., Division of Hematology/Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, 199 Tun Hua North Road, Taipei 105, Taiwan, Republic of China; Fax number: 011-44-886-3-3278211; E-mail: whm526@ms12.hinet.net

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BACKGROUND. To evaluate the efficacy and toxicity of cisplatin, tegafur, and leucovorin as neoadjuvant chemotherapy (CT) for patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck (SCCHN).

METHODS. Patients with SCCHN according to World Health Organization (WHO) performance status of 2 or less and adequate organ function were enrolled. The CT regimen (PTL) was 50 mg/m^2 cisplatin (P) on Day 1, 800 mg per day oral tegafur (T), and 60 mg per day oral leucovorin (L) for 14 days. The CT was administered at outpatient clinics for 14-day cycles. PTL was initiated with the intent of organ preservation and it was continued for a maximum of six cycles before locoregional therapy. Reevaluation after three cycles led to the termination of CT when the response was less than a partial response. CT was discontinued immediately upon evidence of tumor progression or excessive toxicity.

RESULTS. From March 1996 through July 1999, 97 patients were enrolled consecutively. All participants were men with a median age of 56 years (range, 37–70 years). The primary tumor sites were the tongue base, 14, and the hypopharynx, 83. Sixteen percent of the tumors were Stage III, 84% were Stage IV, 62% were Stage T4, and 44% were Stage N2-3. The median number of CT cycles was six. On an intent-to-treat basis, 26 patients (27%) achieved complete responses and 32 patients (33%) achieved partial responses. The overall response rate was 60% (95% confidence interval, 50–70%). The most common toxicities of WHO Grade 3 or higher included (percent of patients): anemia, 8.3%; stomatitis, 6.3%; thrombocytopenia, 3.1%; and vomiting, 3.1%. With a median follow-up period of 3 years, the overall survival and disease-free survival rates were 40% and 38%, respectively. Organ preservation was achieved in 70% (29 of 37) of the surviving patients.

CONCLUSION. The outpatient PTL regimen was a moderately effective and minimally toxic CT for SCCHN. PTL should be studied further in combination with other active agents or radiotherapy for patients with SCCHN. ***Cancer* 2002;94: 2989–95.** © *2002 American Cancer Society.*

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Cisplatin (P) plus 5-fluorouracil (5-FU [F]) is the most common chemotherapy used for patients with squamous cell cancer of the head and neck (SCCHN).[1,2] Reports in the literature have documented that PF chemotherapy is an effective replacement for surgery in patients with SCCHN arising from the larynx and hypopharynx.[3,4] This approach is also feasible and worthy of further testing in oropharyngeal cancer.[5–7] PF chemotherapy followed by definite radiotherapy has also been shown to increase survival and disease-free survival rates in patients with unresectable diseases treated by defi-

nite radiotherapy alone.[8] In randomized trials, the response rate for treatment-naive patients with locally advanced disease varied from 75% to 85%. Complete responses (CR) were seen in 25–35% and primary site CR rates ranged between 35% and 55%.[3,4,8] In Taiwan, 80–90% of our SCCHN patients were betel quid chewers and about one third of them had oral submucous fibrosis (OSF) related to betel quid chewing.[9] Of our patients, 30–40% experienced mucositis that was Grade 3 or higher according to World Health Organization (WHO) cancer staging. These patients developed mucositis from PF chemotherapy and the response rates were unsatisfactory.[9,10] These results stimulated our efforts to improve the efficacy and toxicity profiles of neoadjuvant chemotherapy for our patients with SCCHN.

Tegafur, a prodrug of 5-FU, is hydroxylated and converted to 5-FU by hepatic microsomal enzymes. Clinical development of intravenous (i.v.) tegafur was discontinued in the United States because of the drug's substantial toxic effects on the gastrointestinal system and central nervous system.[11] In Japan, clinical trials using divided-dose schedules of tegafur given orally demonstrated its clinical efficacy and only mild toxic effects. Oral tegafur may mimic protracted, low-dose 5-FU therapy, which has been suggested to be superior to and better tolerated than bolus dosing of 5-FU.[12,13] Tegafur used preoperatively in patients with SCCHN revealed a high concentration of 5-FU in cancer tissues and metastatic lymph nodes. Subsites that showed high concentrations of 5-FU were the nasal-paranasal cavity, tongue, and mesopharynx.[14] An objective response rate of 24% was documented in patients with head and neck cancers.[15] Phase II trials using cisplatin or carboplatin combined with tegafur had comparative efficacy to the PF regimen in untreated patients with SCCHN.[16,17]

Several studies tried to improve the response rate of PF chemotherapy by adding folinic acid to biomodulate the 5-FU effects on thymidylate synthetase. In patients with SCCHN, induction chemotherapy trial of cisplatin, 5-FU, and high-dose i.v. leucovorin (LV [L]) had an 80–90% response rate and a 50–69% CR rate at the primary tumor site.[18,19] However, the toxicities, especially stomatitis and leukopenia, became more intense (Grade 3 or 4, $\geq$30%) and a substantial increment would be anticipated in the Taiwanese population, as well. In contrast to i.v. LV, oral LV has been shown to result in low ratios of *d*/*l*-reduced folates that may be important in maximizing the effectiveness of 5-FU-LV chemotherapy.[20] Repeated dosage of oral LV pharmacologically simulates continuous infusion of LV.[21] To combine with tegafur for protracted treatment, a dose-finding study for toxicity indicated a dose of oral LV in the range of 45–60 mg per day.[22]

Currently, administration of cancer chemotherapeutic agents has shifted from the hospital to outpatient settings. The administration of higher doses of cisplatin (75 mg/m^2 or more) still requires hospitalization for prolonged hydration and management of emesis.[23] Because no evidence of dose dependency of cisplatin activity in advanced SCCHN has been noted,[24] we prescribed cisplatin in the dose of 50 mg/m^2 biweekly. This dosage could be used in an outpatient setting. This article describes the responses and toxicity profiles of an outpatient induction chemotherapy regimen using cisplatin, tegafur, and LV for advanced SCCHN.

MATERIALS AND METHODS

Patient Characteristics

Eligible patients were required to have histologically proven squamous cell carcinoma of the oropharynx or hypopharynx. They were required to have resectable Stage III or IV disease without distant metastasis, no previous treatment, younger than 70 years old, WHO performance status (PS) less than or equal to 2, adequate bone marrow reserve (leukocyte count $\geq$ 4000/μL and platelets $\geq$ 100,000/μL), adequate renal function (serum creatinine $\leq$ 1.4 mg/dL), and adequate liver function (total bilirubin $\leq$ 1.5 $\times$ upper limit of normal [ULN] and serum aspartate aminotransferase and alanine aminotransferase $\leq$ 2.5 $\times$ ULN). Patients who had serious concomitant illnesses (e.g., cirrhosis, angina, or myocardial disease, or intestinal obstruction, malabsorption, or any other condition that restricted the intake of oral medication) were ineligible. Patients fed with nasogastric tubes but without intestinal malabsorption or obstruction were eligible.

All patients were evaluated before therapy in a multidisciplinary clinic for confirmation for staging and treatment planning. Patients were staged using physical examination, flexible fiberoptic equipment, and computed tomography in accordance with criteria established by the American Joint Committee on Cancer in 1992.[25]

Treatment and Evaluation

The chemotherapy regimen (PTL) consisted of cisplatin (P) 50 mg/m^2 administrated by continuous i.v. infusion for 3 hours on Day 1, oral tegafur (T) 800 mg per day on Day 1 through Day 14, and oral LV (L) 60 mg per day on Day 1 through Day 14. All drugs were administered at outpatient clinics and each cycle was repeated every 14 days. Dose escalation was not attempted. 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 hours. Mannitol 30 g was added to the cisplatin solution to ensure adequate urine output. All patients received i.v. antiemetics of serotonin receptor (5-HT3) antagonists (ondansetron 16 mg or tropisetron 5 mg) before cisplatin. Daily doses of dexamethasone 2 mg for 7 days and metoclopramide 30 mg for 14 days were used to minimize the nausea and delayed emesis that would affect the patients' compliance with the oral medications. If there was vomiting of Grade 2 or higher during the previous cycle, oral 5-HT3 antagonists were prescribed for 5 days after cisplatin. Tegafur was supplied as 200-mg capsules and LV was supplied as 15-mg tablets. Both were administered concurrently and divided into four doses. Compliance with oral tegafur was determined by patient reporting.

Dose modification criteria were designed to reduce the doses of tegafur, and the doses of LV were adjusted concurrently with tegafur. Toxicities to chemotherapy were quantified using the WHO criteria and were evaluated once per cycle on the 14th day. For toxic effects of Grade 2 or higher, treatment was withheld for a maximum of 2 weeks until the effects had resolved completely. The duration of the administration of tegafur plus leucovorin was decreased for 3 days for mucositis, diarrhea, or myelosuppression of Grade 2 or higher during the preceding cycle. Failure to resolve these toxicities for more than 2 weeks after completion of the cycle resulted in discontinuation of chemotherapy. No dose reduction of cisplatin was planned if the patient's serum creatinine level was lower than 2.0 mg/dL. Chemotherapy was discontinued if a patient's serum creatinine level was 2.0 mg/dL or higher.

Responses to chemotherapy were quantified by physical examination, flexible fiberoptic equipment, and computed tomography. Responses in the primary sites and the regional nodes were scored separately and the overall responses were based on the worse of the two responses. CR was defined as the disappearance of all clinically evident tumors. Good partial response (PRg) was defined as a decrease of 75% or more in the product of the two greatest perpendicular diameters of all measurable disease. Partial response (PR) was defined as a 50% or more decrease in the product of the two greatest perpendicular diameters of all measurable disease. No response (NR) was defined as any response less than PR, stable disease, progression of disease, or death while on chemotherapy.

After informed consent was obtained, PTL was initiated with the intent of organ preservation and continued for a maximum of six cycles before locoregional therapy. Reevaluation after three cycles led to the termination of chemotherapy if the response was less than PR. PTL was discontinued immediately upon evidence of tumor progression or excessive toxicity.

TABLE 1
Patient Characteristics

Gender	
Male: female	97:0
Age (years)	
Median (range)	56 (37–70)
Primary tumor site	
Tongue base	14
Hypopharynx	83
Performance status	
0	5
1	75
2	17

All patients were intended to receive radiotherapy or concurrent chemoradiotherapy either postoperatively or immediately after chemotherapy in the case of CR or PRg of the primary tumor. Patients were irradiated with megavoltage radiation using conventional fractionation (1 fraction of 1.8–2 Gy, 5 days a week). In the case of definite radiotherapy after chemotherapy, a dose of 46–46.8 Gy was given, followed by a booster dose of 24–26 Gy on the tumor site and on palpable lymph nodes, if present. When delivered postoperatively, the dose given was 46–46.8 Gy followed by a booster dose of 20–24 Gy. In patients who achieved a CR or PRg in the primary tumor after chemotherapy, neck dissection was recommended before radiotherapy for patients who failed to achieve PR in the neck disease. Postradiation neck dissection was performed in all patients who failed to achieve a clinical CR in the neck 6–8 weeks after completion of radiotherapy. Patients whose primary tumor failed to achieve at least a PR after three cycles of chemotherapy or a PRg after six cycles of chemotherapy had to undergo surgery followed by radiotherapy or concurrent chemoradiotherapy.

RESULTS

From March 1996 through July 1999, 97 patients were enrolled consecutively. The characteristics of the population are listed in Table 1 and the stages of tumor nodes are listed in Table 2. They included Stage III for 15 patients (16%), Stage IV for 82 patients (84%), T4 for 60 patients (62%), and N2-3 for 43 patients (44%).

A total of 567 cycles of PTL were administered with a median of 6 cycles per patient. The mean compliance for oral tegafur was 97% (range, 75–100%). Ninety-seven patients were assessable for toxicity. The commonly observed toxicities are summarized in Ta-

TABLE 2
Tumor Node Staging

Tumor/node	0	1	2A	2B	2C	3	Total
1				2	1		3
2		5		3	1	4	13
3	9	1	1	1	7	2	21
4	28	11		10	9	2	60
Total	37	17	1	16	18	8	97

ble 3. Grade 3 and 4 toxicities were mild and most of the scheduled chemotherapy was given without apparent toxicity. One patient with tongue base cancer developed Grade 4 diarrhea during his second cycle of chemotherapy. His tumor regressed completely and he refused subsequent chemotherapy and local therapy. The tumor recurred locally 3 years later and was resolved by radiotherapy. Two more patients did not complete the third cycle of the protocol due to fatigue in one and fatigue and renal insufficiency in the other. Two patients were taken off chemotherapy due to events unrelated to chemotherapy, including hepatitis B reactivation in one, allopurinol-related Stevens-Johnson syndrome in the other. The most common toxicity was macrocytic anemia. In 84 patients with a hemoglobin (Hb) level of 11 g/dL or more before CT, 30 patients (36%) had a peak mean corpuscular volume (MCV) greater than 100 μm^3. The mean increase in MCV was 7.0 $\pm$ 6.4 μm^3, accompanied by Grade 3 anemia (Hb $<$ 8.0 mg/dL) in seven patients (8.3%). Blood transfusion for symptomatic anemia was needed in eight patients (10%).

Of the 97 patients, 94 patients were assessable for responses. Three patients were not reassessed adequately after entry into the study (due to fatigue and because they received three or fewer courses of chemotherapy) and they were included in the analysis as nonresponders. At the primary tumor site, 34 of 97 patients (35%) achieved CR and 32 of 97 patients (33%) achieved PR. CRs of the primary site were more frequent ($P = 0.046$; by Fisher exact test) among patients with PS 0–1 (32 of 80 patients, 40%) than among patients with PS 2 (2 of 17 patients, 12%). There was also a trend toward more CRs ($P = 0.052$, by chi-square test) among patients with T1-2 disease (9 of 16 patients, 56%) than among patients with T3-4 disease (25 of 81 patients, 31%). There was no difference in the CRs with respect to primary site. There was also no difference in the PRgs with respect to primary site, T stage, or PS. In the 60 patients who had palpable lymph nodes, 19 patients (32%) achieved CR and 11 patients (18%) achieved PR. Overall, 26 of 97 patients (27%) achieved CR and 32 of 97 (33%) patients achieved PR, for an overall response rate of 60% (58 of 97 patients).

With a median follow-up of 3 years, the overall survival and disease-free survival rates of the 97 patients was 40% and 38%, respectively. Of the 60 patients who achieved CR or PRg in the primary tumor, 51 patients received radiotherapy immediately after chemotherapy and 9 patients refused radiotherapy. Of the 51 patients who received radiotherapy immediately, the disease-free survival rate was 51% (26 patients) with an organ-sparing rate of 85% (22 patients) in the surviving patients. Three patients underwent salvage neck dissection alone with organ sparing. Of the nine patients who refused immediate radiotherapy after achieving at least PRg in the primary site, one survived and was disease free among three patients who received chemotherapy alone; four patients survived, two of whom were disease free, among the six patients who received local therapy later in the disease progression. Of the 37 patients who failed to achieve at least PRg in the primary tumor, 26 patients underwent surgery and 11 patients received nonsurgical therapy. The overall survival (and disease-free survival) rate was 27% (7 of 26 patients) in the surgical arm and 0% in nonsurgical arm. Overall, organ preservation was achieved in 70% (29 of 37) of the surviving patients.

DISCUSSION

The PF regimen is still the most common chemotherapy used for SCCHN. However, in our betel quid chewing prevalent area, we experienced unsatisfactory response rates and a high proportion of severe mucositis in response to the PF regimen. We developed the PTL regimen with the hope that this regimen would yield better response rates and improved side-effect profiles compared with the conventional PF regimen.

In our previous studies, 103 SCCHN patients with tumors arising from the hypopharynx and oropharynx with similar tumor extent were treated with the PF-based regimen (response rate of 51% with a CR of 11% and 37% Grade 3 or higher mucositis).[9,10] The results presented in this article show that, within the limits inherent to comparison with our previous studies, we were able to preserve the activity of PF with a substantial reduction in toxicity, especially the mucositis. Another advantage of our PTL regimen was outpatient-based chemotherapy administration. SCCHN is the second most common cancer that occurs in Taiwanese men between the ages of 30 and 59 years.[26] Outpatient chemotherapy with low toxicity may minimize the impact of neoadjuvant chemotherapy on the patients' socioeconomic status and avoid deterioration of physical condition before locoregional therapy.

TABLE 3
Toxicity

	567 cycles (%)					97 patients (%)				
	0	1	2	3	4	0	1	2	3	4
Leukopenia	89.4	8.5	1.9	0.2		66.7	22.9	9.3	0.1	
Anemia[a]	60.5	24.0	13.6	1.9		29.8	33.8	28.6	8.3	
Thrombocytopenia	95.5	3.1	0.6	0.8		89.6	4.2	3.1	3.1	
Stomatitis	81.4	12.8	4.9	0.9		51.0	26.1	15.6	6.3	1.0
Vomiting	91.0	7.1	1.3	0.6		71.9	19.8	5.2	3.1	
Renal	95.5	4.1	0.4			86.4	11.5	2.1		
Diarrhea	99.4			0.4	0.2	98.0			1.0	1.0

[a] Of 498 cycles in 84 patients with a hemoglobin level 11.0 mg/dL or higher before chemotherapy.

Our overall response rate of 60% with a CR of 26% was lower than that achieved by PF in randomized Phase III trials of organ preservation.[3,4] Nonetheless, our study enrolled a higher proportion of patients with tumor class T4 (62%) and/or Stage IV (84%) 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. The 40% 3-year survival rate in our patients (most of whom had advanced hypopharyngeal cancer) and the 70% organ-sparing rate in the surviving patients are comparable to the results reported in the literature.[4,27] This may be due to the fact that in the setting of organ preservation, the locoregional therapies following neoadjuvant chemotherapy were still the major determinant of patient survival. Randomized trials and metaanalysis have both demonstrated a survival benefit with concurrent chemoradiotherapy (CCRT) in combined modality approaches for SCCHN.[28,29] As some reports demonstrated,[30,31] we used cisplatin-based CCRT in six patients who were feasible for organ preservation after responding to neoadjuvant chemotherapy. However, its impact on the overall outcome is difficult to assess due to the limited number of patients.

There are some inherent concerns in using oral chemotherapeutic agents. Because tegafur has nearly complete oral bioavailability with a serum half-life of 10 hours and lacks significant first-pass metabolism, it is suitable for oral use.[32] Patients' compliance to oral chemotherapy would have serious implications on treatment. In this article, the compliance according to patient reporting in interviews was 97%, but it was believed to be overestimated.[33] Other methods such as pill counts or tablet bottles with electronic monitors, although still not entirely perfect, may be more accurate for monitoring compliance.[34]

The complexity of the treatment regimen may affect the patients' compliance as well. When tegafur was used daily without a treatment-free period, the daily dose used in the literature was 500 mg/m^2.[35,36] Because the majority of our population has a body surface area of about 1.5–1.6 m^2, the dose was rounded to a fixed dose of 800 mg per day. The modification of the doses according to the toxicity was adjusted by decreasing the number of days of the prescription but not the daily dosage. Although these views seemed feasible in our clinical practice, it was not a view commonly held. In addition, reports in the literature have demonstrated that the compliance of once-daily or twice-daily regimens was similar, and both were better than more frequent daily dosing.[34] Our four-daily dosage prescription may have compromised compliance with our PTL regimen. Considering the pharmacokinetic and toxicity profiles, and the important impact of missing a dose on a once-a-day regimen, a twice-daily regimen may be more suitable for future trials.

Another factor corresponding to a reduction in overall compliance was side effects, especially the emesis.[34] Cisplatin is the strongest emetic agent and delayed emesis may cause serious implications on oral chemotherapy compliance. The prophylactic antiemetic schema used in this report seems satisfactory with emesis of Grade 2 or higher in only 1.9% of all cycles.

Although the common toxicities were diminished, the frequency and magnitude of anemia were unexpected. One report in the literature on the use of tegafur as an adjuvant chemotherapy for stomach cancer mentioned that tegafur may cause macrocytic anemia at the total dose of approximately 100 g.[37] The occurrence of megaloblastic changes in erythrocytes was also documented in a report of prolonged concurrent infusion of 5-FU plus LV and a weekly cisplatin bolus in patients with metastatic colorectal cancer.[38] The serum folate and vitamin B12 levels remained normal in both reports. The mechanisms may have been due to persistent inhibition of thymi-

dylate synthesis and DNA direct toxicity from protracted use of tegafur, which was further potentiated with a combination of cisplatin and LV. Studies of bone marrow with megaloblastic erythropoiesis due to continuous exposure to 5-FU showed that the recovery of marrow to normoblastic hematopoiesis was apparent within 3–5 days after discontinuing 5-FU.[39] This may explain why macrocytic anemia is not mentioned in reports of patients with SCCHN using cisplatin or carboplatin plus tegafur, but without LV, and with 7-day treatment-free periods between each cycle.[16,17] Therefore, the therapeutic schema of PTL may need to be modified for future applications to the palliative setting of long-term use.

Recently, docetaxel and paclitaxel were shown to have inherent antineoplastic activity in patients with SCCHN and as a radiation sensitizer.[40–43] Some trials added taxenes to the PF or PF plus LV achieved considerable improvement of the response rate.[44,45] However, the toxicities were substantially severe, especially neutropenia and stomatitis. The low incidence of hematologic toxicity and stomatitis of PTL may warrant application of this regimen combined with taxenes. Reports in the literature have documented that oral uracil and tegafur (UFT) plus LV was active for patients with SCCHN.[46] The replacement of tegafur with UFT may be worth trying.

In conclusion, the PTL regimen provided comparative efficacy and better toxicity than the PF regimen in our patients. Because this regimen can be used at outpatient clinics, it may make a contribution to patients' quality of life. The minimal toxicity warrants further application of this regimen in trials combining other active agents or radiotherapy in patients with locally advanced SCCHN. However, the moderate response rates suggest that this regimen should still be viewed with caution. Its use outside of a clinical trial is not routinely indicated.

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