Biweekly Paclitaxel, Cisplatin, Tegafur, and Leucovorin as Neoadjuvant Chemotherapy for Unresectable Squamous Cell Carcinoma of the Head and Neck

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BACKGROUND. The goal of the current study was to evaluate the efficacy and toxicity of paclitaxel, cisplatin (P), tegafur (T), and leucovorin (L) as a neoadjuvant chemotherapy (CT) for patients with advanced, unresectable squamous cell carcinoma of the head and neck.

METHODS. From November 1999 to January 2001, 21 consecutive patients (Stage IV, 100%; T4, 86%; and N3, 41%) were treated with paclitaxel-PTL (Day 1: paclitaxel, 120 mg/m^2 intravenous infusion for 3 hours; Day 1: P, 50 mg/m^2; T, 800 mg; and L, 60 mg orally daily over a 14-day cycle). Evaluation after three cycles led to CT termination if primary tumor responses were less than partial responses. Otherwise, paclitaxel-PTL was continued for up to six cycles before commencement of locoregional therapy.

RESULTS. CT responses were analyzed on an intent-to-treat basis. Response rates (RR) for the primary tumors were 81% (17 of 21), with 28.6% (6 of 21) showing a complete response (CR). RR and CR rates for the neck lymph nodes were 85.3% (15 of 18) and 22% (4 of 18), respectively. The combined RR for primary tumors and neck lymph nodes was 81% (95% confidence interval, 62.9–99.3%) with a CR rate of 19%. Grade 3/4 toxicities according to World Health Organization criteria included leukopenia, 19.0%; emesis, 9.5%; asthenia, 9.5%; mucositis, 4.8%; and neuropathy, 4.8%. Both the overall and disease-free survival rates were 14.3% (3 of 21), with a median follow-up of 41 months.

CONCLUSIONS. The relatively low toxicities and encouraging response rates demonstrated in the current study suggested that paclitaxel-PTL merits future trials in the setting of resectable tumors with more favorable characteristics. ***Cancer* 2004; 101:1818–23.** © *2004 American Cancer Society.*

KEYWORDS: head and neck neoplasms, squamous cell carcinoma, paclitaxel, tegafur.

Squamous cell carcinoma of the head and neck (SCCHN; excludes nasopharyngeal carcinoma) accounts for 4–5% of cancer incidence in Taiwan, and is the second most common cancer in male Taiwanese 30–59 years of age.[1] As two-thirds of patients present with Stage III/IV disease, many have tumors that cannot be completely eradicated by surgery. Radiotherapy (RT) has been the only treatment modality for unresectable tumors. However, the therapeutic results are frustrating. Efforts to improve on these disappointing outcomes have included altered schedules of radiotherapy fractionation and the use of systemic chemotherapy (CT) in conjunction with RT.

Neoadjuvant CT is the multimodal treatment schedule that has been explored most extensively. However, meta-analyses of CT effi-

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cacy in patients with head and neck carcinoma have failed to demonstrate a survival advantage for the neoadjuvant approach.[2–5] Proposed explanations for this failure include poor protocol design with an imbalance of prognostic factors, and suboptimal chemotherapeutic combinations. After separate analysis of neoadjuvant CT regimens using cisplatin/5-fluorouracil (5-FU) and alternative regimens, however, Pignon et al.[5] suggested a survival advantage of 5% at 5 years ($P = 0.01$) for cisplatin/5-FU induction CT. For the subset of patients with unresectable SCCHN, Paccagnella et al.[6] demonstrated a survival advantage for neoadjuvant cisplatin/5-FU in a larger patient population. Although, from meta-analysis, survival benefit has only been demonstrated consistently for concurrent chemoradiotherapy (CCRT), the improvement in locoregional control and survival comes at the expense of increases in acute toxicity and late morbidity. After detailed meta-analysis, Pignon et al.[5] concluded that CCRT should remain experimental, particularly when toxicity and cost-to-benefit ratio are taken into account in addition to survival. More active neoadjuvant CT followed by less intensive CCRT may represent one way to optimize treatment outcome in terms of quality of life and tumor control in patients with advanced SCCHN.[7]

We previously reported the results of 14-day cycles of a PTL regimen using 50 mg/m^2 cisplatin (P) on Day 1, oral tegafur (T) 800 mg/day, and leucovorin (L) 60 mg/day in outpatient clinics.[8] We achieved overall and complete response (CR) rates of 60% and 27%, respectively, in 97 patients with advanced SCCHN. Within the limits inherent to comparison with our previous studies,[9,10] this treatment appears able to preserve cisplatin/5-FU activity while offering a substantial reduction in toxicity, especially in terms of mucositis. Further, its moderate efficacy and favorable toxicity profile indicate potential in combination with other new agents in future investigations.

In 2 Phase II trials, single-agent paclitaxel produced overall RR of 35–40% in patients with recurrent, metastatic, or incurable locally advanced SCCHN.[11,12] Given the established activity of paclitaxel, various studies have incorporated the drug into combination schedules with other cytotoxic agents such as carboplatin, ifosfamide, cisplatin, and 5-FU.[13]

Currently, there are studies demonstrating that biweekly paclitaxel and paclitaxel plus cisplatin are active in patients with metastatic breast carcinoma.[14–16] Granulocytopenia, anemia, and neuropathy are the predominant associated toxicities. As the PTL regimen for SCCHN has the side effect of mild neutropenia (1% Grade 3–4), we hypothesize that biweekly paclitaxel in combination with PTL will have a higher therapeutic index than PTL alone as an outpatient neoadjuvant CT for SCCHN.

MATERIALS AND METHODS

Eligibility criteria included the following: histologically proven SCCHN; unresectable tumor status or patient refusal of a recommended total glossectomy; clinically and/or radiologically measurable disease, with no distant metastasis; no previous treatment; age $\leqq$ 70 years; World Health Organization (WHO) performance status $\leqq$ 2; adequate bone marrow reserves (leukocyte count $\geqq$ 4000/μL and platelet count $\geqq$ 100,000/μL); adequate renal function (serum creatinine $\leqq$ 1.4 mg/dL); and adequate liver function (total bilirubin level $\leqq 1.5 \times$ upper limit of normal [ULN] and serum levels of aspartate aminotransferase and alanine aminotransferase $\leqq 2.5 \times$ ULN). Patients fed with nasogastric tubes but without intestinal malabsorption or obstruction were also eligible.

Exclusion criteria included the following: preexisting sensory or motor neurotoxicity $>$ Grade 2 according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC); known hypersensitivity to drugs or compounds containing Cremophor EL; 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; history of other neoplasms, except squamous or basal cell skin carcinoma; and adequately treated in situ cervical carcinoma. The study was reviewed and approved by the institutional review board and informed consent was obtained from each patient. Patients were staged in accordance with criteria established by the American Joint Committee on Cancer in 1998.[17]

The CT regimen (paclitaxel-PTL) consisted of paclitaxel (Bristol-Myers Squibb Co., Princeton, NJ) 120 mg/m^2 continuous intravenous infusion (IVF) for 3 hours followed by P 50 mg/m^2 IVF for 3 hours on Day 1, oral T 800 mg/day on Days 1–14, and oral L 60 mg/day on Days 1–14. All drugs were administered at outpatient clinics, and each cycle was repeated every 14 days and there was no interval between the 14-day cycles.

All patients were intravenously premedicated with 20 mg dexamethasone, 50 mg diphenhydramine, and 300 mg cimetidine at 30 minutes, 1 hour, and 1 hour, respectively, before receipt of paclitaxel. Serotonin receptor (5-HT3) antagonists (16 mg ondansetron or 5 mg tropisetron) were administered before P. Daily doses of 2 mg dexamethasone for 7 days and 30 mg metoclopramide for 14 days were used to minimize the nausea and delayed emesis that could affect patient compliance with the oral medication. T was sup-

plied as 200-mg capsules and L as 15-mg tablets. Both were divided into four doses and administered concurrently. Compliance with oral T was determined by patient self-report.

Toxicities of CT were quantified using the NCI CTC, and evaluated once per cycle on Day 14. For toxic effects of ≥ Grade 2, treatment was withheld for a maximum of 2 weeks until the effects had resolved completely. Failure to resolve these toxicities for > 2 weeks after completion of the cycle resulted in the discontinuation of CT. Dose modification criteria were designed to reduce the dosage of paclitaxel and T in line with hematologic and nonhematologic toxicities, respectively. The paclitaxel dosage was reduced by 10 mg/m^2 when the granulocyte count was < 1500 /μL or the platelet count was < 75,000 /μL, and by 20 mg/m^2 when neutropenic fever or thrombocytopenia was complicated by severe bleeding or when > 2 platelet transfusions were needed. The duration of the administration of the T-L combination was decreased by 3 days for mucositis, diarrhea, or myelosuppression ≥ Grade 2 during the preceding cycle. A maximum of two dose level reductions was allowed per patient. No P dose reduction was planned if the serum creatinine level was < 2.0 mg/dL, but CT was discontinued if the serum creatinine level was ≥ 2.0 mg/dL.

According to the treatment scheme, once three courses of the paclitaxel-PTL had been completed, there was a preliminary evaluation of response to induction treatment by clinical examination and flexible fiberoptic nasopharyngoscopy. This led to termination of CT if outcome was considered to be less than a partial response (PR). Patients who had achieved an initial response (CR or PR) after three courses of CT underwent three more courses. Subsequent treatment consisted of RT or CCRT. Patients with stable or progressive disease after three courses of CT received radical or palliative treatment (e.g., second-line CT, RT) depending on the individual characteristics of each patient.

Responses to CT were quantified in accordance with the WHO criteria by physical examination, flexible fiberoptic equipment, and computed tomography scan. Response at the primary site and response in the regional lymph nodes were scored separately, with the poorer of the two being considered the overall response.

All patients were scheduled to undergo RT or CCRT after neoadjuvant CT. Subjects were irradiated with megavoltage RT using conventional fractionation (1 fraction of 1.8–2 gray [Gy], 5 days a week). A dose of 46–46.8 Gy was given, followed by a booster dose of 24–26 Gy to the tumor site and to palpable lymph nodes, if present. The CT regimen for CCRT was not specified in the design of the trial. Surgical resection was performed for residual lesions, if feasible, 6–8 weeks after completion of RT.

TABLE 1
Patient Characteristics

Gender	
Males:females	20:1
Median age (range) in yrs	43 (34–66)
Primary tumor site	
Oropharynx	10
Tonsil	10
Oral cavity	8
Tongue	5
Buccal	2
Hard palate	1
Hypopharynx	3
Performance status	
0	9
1	11
2	1

TABLE 2
Tumor and Lymph Node Staging[a]

	N status						
T status	**0**	**1**	**2a**	**2b**	**2c**	**3**	**Total**
1						1	1
2							0
3						2	2
4	3	3	1	4	2	5	18
Total	3	3	1	4	2	8	21

[a] Totals: T4, 18 of 21 patients (86%); N3, 8 of 21 patients (41%); Stage IV, 21 of 21 patients (100%).

RESULTS

Twenty-one consecutive patients were enrolled in the study between November 1999 and January 2001. The characteristics of the population are summarized in Table 1, and data on tumor and lymph node status are presented in Table 2. All 21 patients in the current study had Stage IV disease; 18 patients (86%) had T4 tumors, and 8 (41%) had N3 lymph node status. Disease was classified by the attending surgeon as being unresectable due to the presence of a massive and infiltrative primary tumor (n = 16); large, fixed neck lymph nodes (n = 3); or advanced-stage tongue carcinoma (n = 2).

A total of 113 cycles of paclitaxel-PTL were administered, with a mean of 5.38 cycles per patient. The reasons for early discontinuation were neuropathy ≧ NCI CTC Grade 2 in 2 patients, and expiry due to aspiration pneumonia in 1 patient. Eleven subjects required a delay in scheduled CT by a mean of 2

TABLE 3
Toxicity Data

	% of 21 patients				
Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	33.3	9.5	38.1	9.5	9.5
Anemia	0.0	61.9	33.3		4.8
Thrombocytopenia	100.0				
Stomatitis	28.6	23.8	42.9	4.8	
Emesis	61.9	23.8	4.8	9.5	
Renal toxicity	95.2	4.8			
Diarrhea	85.7	9.5	4.8		
Liver toxicity	76.2	19.0	4.8		
Neurotoxicity	61.9	28.6	4.8	4.8	
Fatigue	57.1	23.8	9.5	9.5	

weeks. The reasons for the delayed administration were renal insufficiency ($n = 1$), stomatitis ($n = 1$), asthenia ($n = 1$), and myelosuppression ($n = 9$). The mean compliance for oral T for the 21 patients was 96.4 ± 6.7% (range, 75–100%).

Toxicities are presented in Table 3. The most common toxicities of ≥ Grade 3 were leukopenia, 19.0%; emesis, 9.5%; asthenia, 9.5%; mucositis, 4.8%; and neuropathy, 4.8%. No neutropenic fever was noted. One patient experienced transient chest tightness and dyspnea during paclitaxel infusion in the first cycle. Hospitalization was required for 2 patients experiencing Grade 3 asthenia, with subsequent death due to the effects of sepsis with disease progression in one patient and apparent tumor regression in the other.

Of the 21 patients, 20 were assessable in terms of treatment response. One patient died of aspiration pneumonia after his second cycle of CT without adequate reassessment of his response and was included in the analysis as a nonresponder. At the primary tumor site, a CR was achieved by 6 of 21 patients (28.6%) and a PR was achieved by 11 patients, giving an overall RR of 81.0% (17 of 21). Of the 18 patients with neck lymph node metastases, a CR was achieved by 4 (22.2%) and a PR by 11 (61.1%). From intent-to-treat analysis, the combined tumor/lymph node CR rate was 19.0% (4 of 21) and the overall RR was 81% (17 of 21; 95% confidence interval, 62.6–99.3%).

Three patients did not receive RT after paclitaxel-PTL due to premature death from aspiration pneumonia ($n = 1$) and patient refusal of RT ($n = 2$). Of the remaining 18 individuals, 17 and 1 underwent CCRT and RT, respectively. The CT regimens for CCRT were 200 mg/m^2 gemcitabine weekly ($n = 11$), PTL ($n = 5$), and 40 mg/m^2 paclitaxel weekly ($n = 1$). The overall and disease-free survival rate for the 21 patients was 14.3% (3 of 21), with a median follow-up of 41 months (range, 34–48 months).

DISCUSSION

Paclitaxel and docetaxel have similar and encouraging efficacies, with a 30–35% single-agent RR demonstrated for recurrent/metastatic SCCHN.[11,18] Taxane combinations have been the focus of SCCHN investigations. However, only limited data were available with respect to the combination of paclitaxel and cisplatin/5-FU in advanced SCCHN. Overall and CR rates of 33% and 5%, respectively, were achieved in a Phase I–II trial of 18 patients with recurrent and/or metastatic SCCHN (paclitaxel 100–160 mg/m^2 by 3-hour IVF on Day 1 combined with cisplatin 20 mg/m^2 on Days 1–3 and 5-FU 200 mg/m^2 bolus IVF on Days 1–3 every 3 weeks).[19] Hussain et al.[20] used paclitaxel 135 mg/m^2 delivered by 3-hour IVF on Day 1, cisplatin 75 mg/m^2 on Day 2, and 5- FU 4 g/m^2 over 4–5 days every 3 weeks in 25 patients with recurrent, advanced, or metastatic SCCHN. The RR for the 6 locally advanced, treatment-naive patients was 66%, with a CR rate of 16%. Hainsworth et al.[21] utilized paclitaxel 200 mg/m^2 by 1-hour IVF on Days 1 and 22, carboplatin area under the concentration curve (AUC) of 6.0, and 5-FU 225 mg/m^2 per day by 24-hour continuous IVF on Days 1–35 every 6 weeks in a sample of 7 patients with locally advanced, treatment-naive SCCHN. The six responders included four who experienced a CR. Although these 3-drug combinations were feasible, toxicities were moderately severe with Grade 3–4 myelosuppression and mucositis occurring in 40% and 30% of the patients, respectively. In comparison to these trials, in our study, besides the encouraging activity, paclitaxel-PTL has the advantages of relatively low toxicity and outpatient administration. The 14.3% overall and disease-free survival rate over a median follow-up of 41 months (range, 34–48 months) was comparable to reports for unresectable or inoperable patients.[6,22]

Paclitaxel is generally administered every 3 weeks (175 mg/m^2 over 3 hours or 135 mg/m^2 over 24 hours). Biweekly paclitaxel 90 mg/m^2 IVF over 3 hours and cisplatin 60 mg/m^2 have been tested in patients with advanced-stage and/or metastatic SCCHN.[23] The RR of 33% was similar to that expected using the cisplatin/5-FU regimen. The major toxicity was neutropenia ≧ grade 3, which occurred in 52% of the cycles, and the median dose intensity was 39 mg/m^2 per week for paclitaxel and 26 mg/m^2 per week for cisplatin. Although a higher dose of paclitaxel was used in our trial (biweekly 120 mg/m^2), there were neutropenia ≧ Grade 3 in 6% of the cycles and neurotoxicity ≧ Grade 2 in 9.6% of the patients. In the literature, more limited neurotoxicity was reported for the above biweekly paclitaxel/cisplatin regimen for the treat-

ment of metastatic breast carcinoma relative to the triweekly analog.[14–16] However, these toxicities were higher than for single-agent paclitaxel (150 mg/m^2 biweekly).[24] It has been suggested that cisplatin is the major contributor to the toxicity associated with the cisplatin-paclitaxel combination. The lower cisplatin dosage (biweekly 50 mg/m^2) used in our trial may be attributable to the lower toxicities achieved when higher dosages of paclitaxel and T/L were combined.

In the current study, the paclitaxel dose translated to a dose intensity of 60 mg/m^2, or was equivalent to the 3-week dosage of 180 mg/m^2. This was equivalent to a dosage of 175 mg/m^2 infused over 3 hours and exceeded that used in the biweekly trials of breast carcinoma. Can the efficacy be improved further by escalating the paclitaxel dosage? A randomized study of advanced-stage SCCHN that used cisplatin (75 mg/m^2) plus paclitaxel (135 or 200 mg/m^2 infused over 24 hours) demonstrated no significant difference in the RR (35% vs. 36%, respectively) or median survival times.[25] A literature review for other solid malignancies in a palliative setting also demonstrated that dose-intense paclitaxel generated significantly higher RR but did not improve survival. In the palliative setting, there seems to be little increase in efficacy for escalating the paclitaxel dose beyond 175 mg/m^2 infused over 3 hours or 135 mg/m^2 infused over 24 hours every 3 weeks.[26] Given the results of this and other studies, it seems reasonable to suggest that it is appropriate to retain the current dosage of paclitaxel for palliative therapy in patients with SCCHN with a poor prognosis. Given its relatively low toxicity, however, future treatment trials for resectable SCCHN should investigate the potential for improvement in therapeutic results with increased paclitaxel dose in a neoadjuvant setting. A recent trial of 6 weekly doses of paclitaxel (135 mg/m^2) and carboplatin (AUC2) followed by CCRT in advanced-stage SCCHN achieved encouraging results of a PR rate of 52% and a CR rate of 35% in the neoadjuvant setting.[27]

One potential conflict of the paclitaxel-PTL regimen is the sequence-dependent antagonism between 5-FU and paclitaxel. In vitro assays have demonstrated that preexposure with 5-FU followed by paclitaxel resulted in marked antagonism, with sequential paclitaxel followed by 5-FU being optimal.[28,29] It was suggested that this was a consequence of 5-FU preexposure producing S-phase accumulation and diminished paclitaxel-associated G_2/M-phase block, whereas subsequent exposure to 5-FU after paclitaxel did not diminish paclitaxel-associated G_2/M-phase block. Continuous administration of the oral 5-FU prodrug (T) in our trial may have resulted in sequence-dependent antagonism of paclitaxel, leading to reduced efficacy for these two-drug combinations in clinical CT. However, promising results have still been demonstrated for paclitaxel in combination with continuous 5-FU infusion and RT in SCCHN.[21, 30] The significance of the sequence-dependent antagonism between 5-FU and paclitaxel needs further examination. As p53 and p21 return to basal levels 24 hours after transient induction of increases by 5-FU exposure subsequent to removal, transient omission of T between CT cycles may potentially improve the results of future trials.[29]

Optimization of the dosage and schedule for taxane combination regimens in a palliative or curative setting remains the subject of ongoing SCCHN treatment trials. Substantial and significant survival gains have yet to be demonstrated for taxane-based therapies in comparison to the cisplatin/5-FU analogs. The relatively low toxicities, outpatient administration, and encouraging RR suggest that paclitaxel-PTL merits future trials in a setting defined by resectable tumors with more favorable characteristics.

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