High Rate of Clinical Complete Response to Weekly Outpatient Neoadjuvant Chemotherapy in Oral Carcinoma Patients Using a New Regimen of Cisplatin, 5-Fluorouracil, and Bleomycin Alternating with Methotrexate and Epirubicin

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BACKGROUND. A Phase II trial was initiated to evaluate the response to and toxicity of a new regimen of weekly outpatient neoadjuvant chemotherapy in patients with oral carcinoma.

METHODS. Patients with previously untreated squamous cell carcinoma of the oral cavity were eligible for this trial. The neoadjuvant chemotherapy was comprised of cisplatin, 25 mg/m^2, 5-fluorouracil, 1000 mg/m^2, and bleomycin, 10 mg/m^2, mixed in normal saline as a 24-hour intravenous (i.v.) infusion, alternating with methotrexate, 30 mg/m^2, and epirubicin, 30 mg/m^2, as an i.v. bolus (PFB/ME) on a weekly schedule for 8–12 weeks. In patients with American Joint Committee on Cancer Stage IV disease who completed neoadjuvant chemotherapy, surgery was preferred to radiotherapy, unless patients refused surgery.

RESULTS. A total of 40 patients (82.5% with Stage IV disease) with previously untreated oral carcinoma were enrolled. The median size of the primary tumor was 7 cm (range, 3–13 cm). Fifty percent of patients had tumor penetrating through the oral mucosa to the cheek skin and 62.5% had bony destruction. Detectable cervical lymph nodes were noted in 77.5% of patients. After neoadjuvant weekly chemotherapy, 22 patients (55%) showed complete response (CR) and 15 patients (37.5%) showed partial response, for an overall response rate of 92.5%. World Health Organization Grade 3/4 toxicity included mucositis (7.5%), leukopenia (25%), anemia (10%), and thrombocytopenia (2.5%). Eleven of 33 patients with Stage IV disease underwent surgery, and pathologic CR (2 patients) or microscopic residual tumor (4 patients) was noted (54.5%).

CONCLUSIONS. The results of the current study indicate that a weekly PFB/ME neoadjuvant chemotherapy regimen is highly effective for the treatment of patients with oral carcinoma. In addition, this regimen has low toxicity. The authors believe that implementation of this regimen into a multimodality therapy protocol deserves further study. *Cancer* 1999;85:1430–8. © 1999 American Cancer Society.

KEYWORDS: oral carcinoma, weekly, neoadjuvant, chemotherapy.

Carcinoma of the oral cavity can affect the upper and lower lips, gingivobuccal sulcus, buccal mucosa, upper and lower gingiva, hard palate, floor of the mouth, and anterior two-thirds of the mobile tongue. Although early stage oral carcinoma is highly curable by either surgery alone or radiotherapy alone, the treatment results in patients with locoregionally advanced oral carcinoma are disappointing. Surgery combined with radiotherapy is considered the standard

therapeutic approach for advanced disease without distant metastases. The cure rate for resectable disease is approximately 40%, but can fall below 20% for unresectable disease.[1–6] The major pattern of failure after surgery and/or radiotherapy is persistent or recurrent locoregional disease. Local control may be improved by increasing the radiation dose, but high doses of radiation to critical organs are associated with high rates of late morbidity.

Oncologists have sought to improve local control and survival by combining chemotherapy with standard treatment in patients with advanced solid tumors.[7–10] Both neoadjuvant chemotherapy (before surgery or radiotherapy) and concomitant chemotherapy (with radiotherapy) for head and neck tumors have been studied extensively during recent years.[3–6,9–45] However, there still is great controversy regarding the optimal timing, dosage, and contribution of chemotherapy to increase curability. Weekly chemotherapy is a new method of drug delivery that has become more popular in the treatment of various tumors in recent years. In April 1993, a prospective Phase II study was initiated to evaluate the compliance, response, and toxicities of an outpatient, weekly neoadjuvant chemotherapy regimen of cisplatin, 5-fluorouracil, and bleomycin (PFB) alternating with methotrexate and epirubicin (ME) for the treatment of patients with advanced oral carcinoma.

PATIENTS AND METHODS

Patients with previously untreated oral carcinoma were eligible for this study. The minimal entry criteria were 1) pathologic documentation of squamous cell carcinoma from primary tumor biopsy; 2) Karnofsky performance status $\geq$ 50%; 3) pretreatment leukocyte count $>$ 3000/mm^3 and platelet count $>$ 100,000/mm^3; 4) serum creatinine level $<$ 2.0 mg/dL; 5) normal bilirubin ($<$2.5 mg/dL); and 6) obtainment of informed consent.

Treatment Planning
All patients received a subcutaneous implanted port insertion, and chemotherapy was delivered in an outpatient setting. The weekly chemotherapy regimen was comprised of cisplatin, 25 mg/m^2, plus 5-fluorouracil, 1000 mg/m^2, plus bleomycin, 10 mg/m^2 (PFB) mixed in 100–150 mL of normal saline delivered by 24-hour continuous intravenous (i.v.) infusion via an ambulatory infusion pump, alternating with methotrexate, 30 mg/m^2, i.v. bolus plus epirubicin, 30 mg/m^2, i.v. bolus (ME). The weekly chemotherapy session was delayed if World Health Organization Grade 3–4 toxicity developed, and resumed after recovery. No dose reduction was allowable. Chemother-

apy was to be discontinued in patients who had no response after 4 weeks of treatment or who refused treatment. A total treatment duration of 3 months (12 weekly chemotherapy sessions) originally was planned, but a minimum of 8 weeks of chemotherapy also was considered acceptable before local therapy. After neoadjuvant chemotherapy, if the tumor was resectable, surgical resection was preferred to radiotherapy, unless patients refused or their medical condition prohibited surgery. If the tumor still was unresectable after chemotherapy, radiation therapy $\geq$ 70 gray (Gy) was planned. For patients who underwent surgery, postoperative radiotherapy was omitted if no viable tumor or small residual tumor was present microscopically.

Evaluation of Treatment
All patients were assessed routinely once a week, including the clinical evaluation of any treatment-induced symptoms/signs, inspection and palpation of the primary tumor and cervical lymph node(s), measurement of body weight, complete blood count, and platelet count. Renal and liver functions were evaluated once a month. Computed tomography (CT) scan was repeated after 8 weeks of chemotherapy or between the completion of neoadjuvant chemotherapy and the initiation of local treatment.

Objective responses were assessed according to World Health Organization (WHO) criteria.[46] Complete response (CR) was defined as the complete disappearance of all clinical and radiographic evidence of disease at the time of objective reevaluation, determined by 2 observations no $<$ 4 weeks apart. Partial response (PR) was defined as a $\geq$ 50% decrease in the sum of the products of the greatest dimensions of all measurable lesions from 2 observations no $<$ 4 weeks apart. Included in the definition of PR were no new lesions or the progression of any existing lesions. Stable disease (SD) was defined as a reduction in tumor size less than PR and an increase in tumor size less than that defined as progressive disease (PD) or no response. PD was defined as a $\geq$ 25% increase in total tumor size of $\geq$ 1 lesions, or the appearance of a new lesion. Toxicity also was evaluated according to WHO criteria.[46]

Follow-Up
Patients underwent a clinical check-up every 2–3 months in the first 2 years after completion of treatment, at 6-month intervals between the third and fifth years, and annually thereafter. CT scan was repeated every 6 months during first 2 years, annually after 2 years, or at any time when recurrence was suspected.

TABLE 1
Patient Characteristics

Characteristic	No.	%
Gender		
Male:female	36/4	
Age (yrs)		
Median (range)	58 (30–82)	
Prechemotherapy Karnofsky scale		
90	4	10.0
80	24	60.0
70	10	25.0
60	1	2.5
50	1	2.5
Pathology: all squamous cell carcinoma		
Well differentiated	9	22.5
Moderately differentiated	30	75.0
Poorly differentiated	0	0
Not mentioned	1	2.5
Primary site		
Buccal	27	67.5
Gingiva	5	12.5
Tongue	4	10.0
Hard palate	4	10.0
T classification		
T4	33	82.5
T3	3	7.5
T2	4	10.0
N classification		
N0	9	22.5
N1	2	5.0
N2	25	62.5
N3	4	10.0
AJCC/UICC stage grouping		
IV	33	82.5
III	4	10.0
II	3	7.5

AJCC: American Joint Committee on Cancer; UICC: International Union Against Cancer.

RESULTS
Patient Characteristics
Between April 1993 and March 1997, a total of 40 patients with previously untreated oral carcinoma were enrolled. Patient characteristics are shown in Table 1. The majority of patients (82.5%) presented with American Joint Committee on Cancer Stage IV disease.[47] The median size of the primary tumor was 7 cm (range, 3–13 cm). Approximately 50% of patients presented with facial skin invasion (Fig. 1A) and 62.5% with bony destruction. Cervical lymph nodes were detected in 31 patients (77.5%).

Patient Compliance and Actual Dose Delivery
Thirty-four of the 40 patients completed the planned 8–12 weeks of chemotherapy. The remaining six patients completed three, four, five, five, six, and six doses of chemotherapy, respectively. The causes of premature interruption were no response (three patients), patient refusal to continue due to toxicity (two patients), and unknown (one patient) (patient was lost to follow-up with a tumor PR and without obvious side effects). In 31 patients, treatment was not delayed. In 7 patients, treatment was delayed for 1 week due to leukopenia (four patients), mucositis (one patient), leukopenia plus mucositis (one patient), and patient refusal (one patient). Treatment was delayed for 2 weeks due to leukopenia (1 patient), and was delayed for 9 weeks for 1 patient. The total interruption for 9 weeks was due to acute hepatitis, pancytopenia, and mucositis. By the time this patient underwent surgical resection, the tumor status had deteriorated from CR to PR. As of June 1997, a total of 412 weekly doses had been delivered to 40 patients, with a mean of 10.3 doses.

Tumor Response and Toxicity
All 40 patients had measurable lesions for response evaluation. After neoadjuvant chemotherapy, we observed 22 patients with CR (55.0%), 15 with PR (37.5%), and 3 with SD (7.5%), for an overall response rate of 92.5% (Table 2). Figure 1B shows CR in a original, huge buccal tumor after 10-week PFB/ME neoadjuvant chemotherapy; the CR was proven by series section of the resected lesion pathologically.

Toxicity usually was mild and well tolerated. Some patients experienced mild anorexia and a sensation of weakness during the chemotherapy infusion, which lasted for several hours. WHO Grade 3–4 toxicity incidences included leukopenia (25.0%), anemia (10.0%), thrombocytopenia (2.5%), and mucositis (7.5%). Patients recovered from toxicity effects soon after transient discontinuation of chemotherapy infusion. Four patients experienced Grade 1 nausea/emesis during chemotherapy. There was no diarrhea or renal or liver function impairment, except for one patient who developed an acute hepatitis B attack with marked hepatic dysfunction. Body weight loss during chemotherapy occurred in only 13 patients (32.5%). The majority of patients experienced improved oral intake due to rapid tumor regression, resulting in weight gain (40%) or stable body weight (27.5%). Table 3 lists the acute toxicity incidences.

Further Treatment and Outcome after Neoadjuvant Chemotherapy
Surgery was not recommended after neoadjuvant chemotherapy for seven patients with Stage II or Stage III disease (six patients with CR and one patient with SD), and they received local radiotherapy. At last follow-up, among the 6 patients with CR, 2 patients with carcinoma of the hard palate developed tumor recurrence
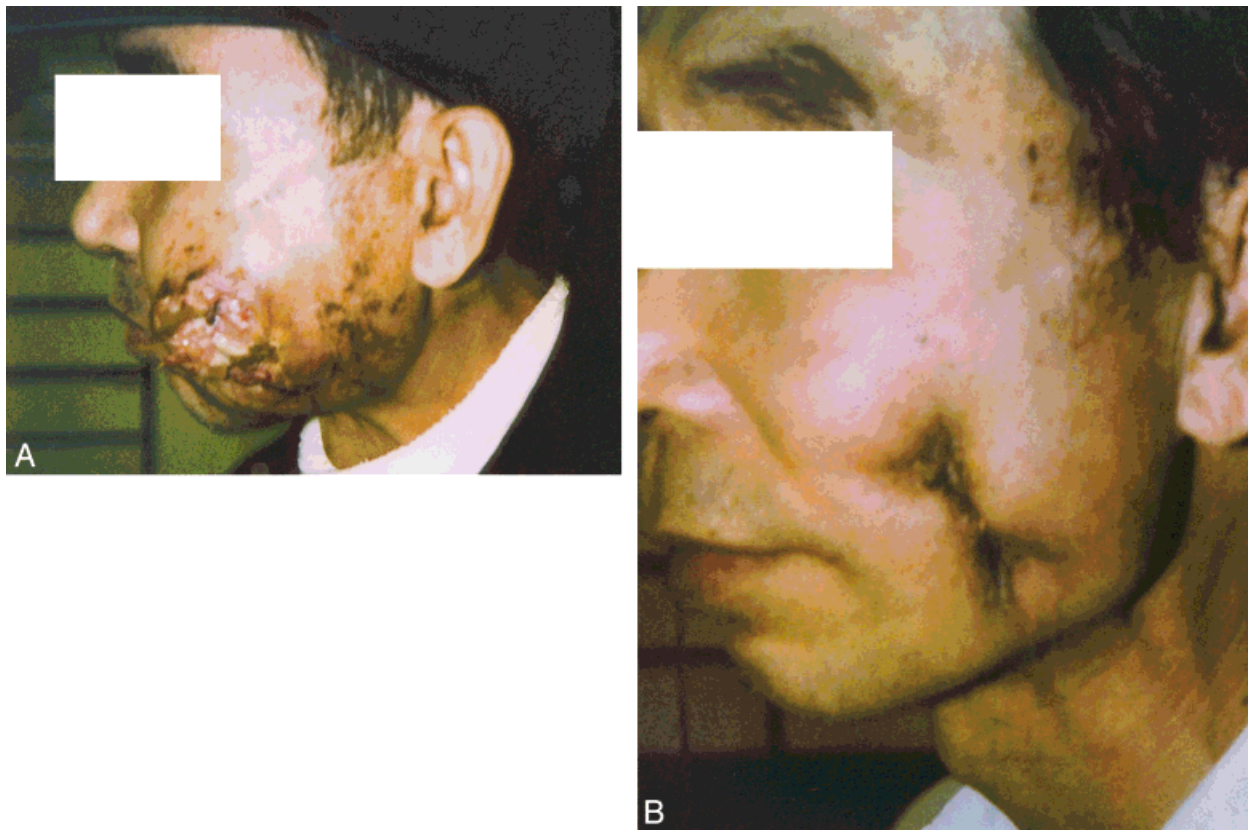
FIGURE 1. Photographs of a patient with a bulky tumor penetrating through the oral mucosa to the facial skin before chemotherapy (A), which disappeared completely after neoadjuvant chemotherapy (B). The resected specimen showed no tumor under thorough microscopic examination.

TABLE 2
Tumor Response (N = 40) after Neoadjuvant Chemotherapy

Response	No. of cases	(%)
CR	22	55.0%
PR	15	37.5%
SD	3	7.5%
PD	0	0

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

and died, and 4 patients with buccal carcinoma were still alive with no evidence of disease (NED) for a mean duration of 46 months (range, 44–51 months). An 82-year-old female with T3N0M0 buccal carcinoma had SD after 4 weekly neoadjuvant chemotherapy sessions, and switched to concomitant chemoradiotherapy. Although her tumor disappeared completely, Grade 4 mucositis developed, and she died of malnutrition.

Eleven of the 33 patients with Stage IV disease (6 with CR and 5 with PR) underwent radical resection. Two patients with CR and four patients with small residual microscopic tumor were noted under thorough pathologic examination. Postoperative adjuvant radiotherapy was omitted for five patients. Four of these 5 patients were still alive with NED at a mean duration of 45 months (range, 24–60 months). One patient with pathologically near CR received postoperative radiotherapy (50 Gy/25 fractions in 5 weeks) and was still alive without tumor recurrence at 48 months of follow-up but had developed osteonecrosis. Four patients had tumor recurrence before planned adjuvant radiotherapy and all had died of disease at last follow-up.

Thirteen patients (8 with CR and 5 with PR) with Stage IV disease refused surgery, requesting radiation therapy instead. The outcomes were poor; 5 patients experienced local recurrence, 1 developed distant metastases, and 2 died of severe mucositis and malnutrition within 1 month after radiotherapy. One patient died of causes unrelated to carcinoma. Only 4 patients were alive with NED at a mean duration of 29 months range, 17–49 months). The tumor extensions of these 13 patients were less bulky and less invasive than the 11 patients who received surgery, e.g.: 1) the median

TABLE 3
Acute Toxicity (N = 40)

| Grade	0	1	2	3	4
Leukopenia	11 (27.5%)	13 (32.5%)	6 (15.0%)	6 (15.0%)	4 (10.0%)
Anemia	14 (35.0%)	9 (22.5%)	13 (32.5%)	2 (5.0%)	2 (5.0%)
Thrombocytopenia	34 (85.0%)	2 (5.0%)	3 (7.5%)	1 (2.5%)	0 (0.0%)
Mucositis	26 (65.0%)	3 (7.5%)	8 (20.0%)	2 (5.0%)	1 (2.5%)
Weight loss	27 (67.5%)	9 (22.5%)	4 (10.0%)		
Alopecia	1 (2.5%)	10 (25.0%)	19 (47.5%)	10 (25.0%)	
Nausea/emesis	36 (90.0%)	4 (10.0%)			
Diarrhea	40 (100%)				
Elevated BUN/Cr	40 (100%)				

BUN: blood urea nitrogen; Cr; creatinine.

and mean sizes of the primary tumor were 8 cm and 8.6 cm, respectively, in the chemosurgery group and were 6 cm and 6 cm, respectively, in the chemoradiotherapy group; 2) the incidence of bony invasion was higher in the chemosurgery group (10 of 11 patients) than in the chemoradiotherapy group (5 of 13 patients); and 3) the incidence of facial skin involvement was higher in the chemosurgery group (7 of 11 patients) than in the chemoradiotherapy group (3 of 13 patients). Thus, comparison of the final outcomes between chemosurgery and chemoradiotherapy appears to be inappropriate.

Six patients (four with PR and two with SD) with Stage IV disease and very extensive tumor invasion were not recommended for surgery. They all died of PD or massive tumor bleeding, although five of the six patients had received radiotherapy (three patients could not complete the planned radiation dose). Two patients with Stage IV disease who achieved clinical CR after neoadjuvant chemotherapy refused surgery and radiotherapy. They had rapid tumor regrowth at 2 and 3 months, respectively, and died. Another patient with Stage IV disease was lost after 6 weekly neoadjuvant chemotherapy doses with tumor PR.

Figure 2 summarizes patient treatment pathways and outcomes after chemotherapy.

DISCUSSION

The standard treatment for advanced squamous cell carcinoma of the head and neck region (SCCHN) without distant metastases is surgery plus postoperative radiotherapy. However, prognosis is poor, and has improved very little over the last 20 years. Chemotherapy can be incorporated into a conventional surgery/radiotherapy program in three different ways: before (neoadjuvant), during (concomitant), or after (adjuvant) locoregional therapy. Postradiation or postoperative adjuvant chemotherapy seldom is tried because
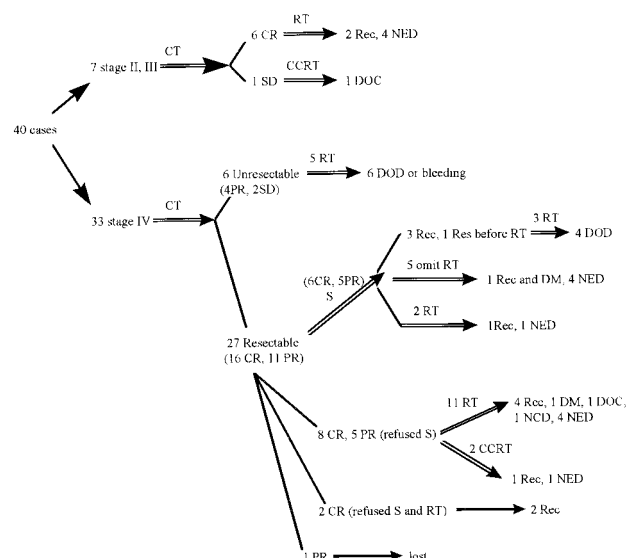
FIGURE 2. Tree diagram of treatment pathways after neoadjuvant chemotherapy and final outcomes. CT: chemotherapy; RT: radiotherapy; CCRT: concomitant chemoradiotherapy; S: surgery; CR: complete response; PR: partial response; SD: stable disease; Rec: recurrent; Res: residual; DM: distant metastasis; DOD: died of disease; DOC: died of complication; NCD: noncarcinoma death; NED: no evidence of disease.

compromised vasculature, caused by radiation change or ablative surgery, will reduce drug penetration and the effectiveness of chemotherapy. The majority of clinical trials involve either neoadjuvant or concomitant chemotherapy for advanced SCCHN.[3–6,9–45] In general, the disadvantages of neoadjuvant chemotherapy include delayed primary treatment in nonresponders, refusal of further curative therapy in responders, triggering of accelerated repopulation of surviving clonogens,[48] and cross-resistance to further radiotherapy. The major disadvantage of concomitant chemotherapy are increasing toxicity when two treatment modalities are delivered simultaneously. In ad-

dition, the dose intensity of concomitant chemotherapy usually is less than that of neoadjuvant chemotherapy, resulting in some decline in killing effect. For SCCHN, neoadjuvant chemotherapy, which was very popular in the 1980s, appears to have been replaced gradually by concomitant chemotherapy in the 1990s in clinical trials. However, a recent survey has reported that neoadjuvant chemotherapy for advanced SCCHN has become a dominant community standard of practice in the U.S.[49]

This Phase II trial was based on several reasonable and unique considerations. First, we confined the entry patients to those with oral carcinoma only. SCCHN refers to a heterogeneous population of patients with a primary tumor arising from the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, nasal cavity, paranasal sinus, etc. There are substantial discrepancies in terms of treatment outcome between the various anatomic subsites.[17,40,42] Second, it has been well established that tumor cell heterogeneity exists in fresh tumor biopsies and long term cell culture lines. Cells within a solid tumor may differ in many properties, including morphology, metabolic characterization, antigenic potential, karyotype, cell surface receptors, drug and radiation sensitivity, and ability to metastasize.[50–56] To combat different tumor cells, we chose a combination of five drugs. Each drug has been demonstrated to be an effective agent in SCCHN. Third, the drug delivery schedule differed from convention: weekly, alternating PFB with ME in an outpatient setting. The expected advantages were reductions in drug resistance, toxicity, and economic cost. Fourth, after neoadjuvant chemotherapy, we preferred surgery to radiotherapy for patients with stage IV disease, even in those in clinical CR. It has been well established that accelerated repopulation[48] and crossresistance of the surviving clonogens are significant causes of failure of radiotherapy administered after induction chemotherapy, resulting in no difference benefit between radiotherapy alone and induction chemotherapy plus sequential radiotherapy. We believe surgery after induction chemotherapy can avoid the problems of accelerated repopulation and crossresistance. Fifth, we recommended patients undergo surgery and postoperative radiotherapy be omitted if surgical pathology shows CR or only microscopic residual tumor after neoadjuvant chemotherapy to avoid radiation-induced morbidity, such as trismus.

Our unique weekly PFB/ME neoadjuvant regimen for patients with advanced oral carcinoma produced encouraging results. A high complete response rate of 55% and an overall response rate of 92.5% were obtained with low toxicity. Patient compliance to our weekly neoadjuvant chemotherapy schedule was bet-

ter than for a conventional monthly schedule of cisplatin, 100 mg/m^2, on Day 1 and 5-fluorouracil, 1000 mg/m^2/day, as a continuous i.v. infusion for 4–5 days, repeated every 3–4 weeks.[5,6,11–23] In recent years, leucovorin has been added to enhance the response rate of this monthly protocol.[24–28] The average overall response rate for the conventional chemotherapy regimen is approximately 85% and the CR rate is approximately 20–40%.[5,6,11–21,26–28] Toxicity is moderate to high, and includes mucositis, bone marrow suppression, and severe alopecia. A substantial percentage of patients will interrupt chemotherapy prematurely or require reduction of the dose intensity, and occasional treatment-related mortalities do occur. In this study, using an unconventional weekly chemotherapy schedule, pathologic findings of 11 patients with bulky Stage IV disease who underwent surgical resection showed no tumor in resected specimens from 2 patients and only very tiny foci of residual viable tumor cells after thorough microscopic examination in 4 patients.

Although a high response rate and low toxicity were achieved using our weekly PFB/ME regimen, there are some problems that remain to be resolved. First, the response duration was brief. Two patients with clinical CR who refused surgery/radiotherapy developed tumor recurrence 2 months and 3 months, respectively, after chemotherapy discontinuation. One patient with CR and 2 with PR received surgery > 1 month after chemotherapy discontinuation and developed tumor recurrence or some degree of disease progression. Second, although compliance to our neoadjuvant chemotherapy program was rather good, some patients refused the planned surgery, even after our attempted persuasion. Third, the final outcomes of Stage IV patients who did not undergo surgery were unsatisfactory. All patients who refused surgery (three patients) or were justified as having inoperable disease (six patients) after neoadjuvant chemotherapy died soon after discontinuation of chemotherapy, even though radiotherapy was administered. Among 13 responders with resectable tumor who refused surgery and received radiotherapy, 6 patients failed treatment and died (5 with local recurrence and 1 with lung metastases), and another 2 patients died of severe mucositis and malnutrition, respectively, within 1 month after the completion of radiotherapy.

Modifications to our weekly PFB/ME protocol should be considered. Increasing dose intensity or adding more drugs is feasible because of the low toxicity of original regimen. We now have experience and evidence from our preliminary trials with which to persuade patients more effectively to undergo planned postchemotherapy surgery. We believe that

the optimal timing of surgery is approximately 1–2 weeks after chemotherapy discontinuation. This is feasible and safe because of the relatively low toxicity of our weekly schedule. For patients who refuse surgery or in whom postoperative adjuvant radiotherapy is justified, we will consider accelerated or hyperfractionated radiotherapy to overcome the phenomenon of accelerated repopulation. Although the recent trend of SCCHN management favors concomitant chemoradiotherapy over neoadjuvant chemotherapy, we still believe that chemotherapy before surgery or radiotherapy deserves to be tried in view of best host tolerance and good vascularity. The majority of clinical trials have concluded that no differences in benefits, in terms of local control or survival, exist between neoadjuvant chemotherapy plus radiotherapy and radiotherapy alone. However, we must point out that subgroup analysis usually demonstrates superior results for responders (especially CR).[20–22,29,30] The key is to create a new protocol with a higher CR rate because the frequently reported CR rate in the majority of regimens is only approximately 20–40%.[5,6,11–21,26–31,33,34,42]

Our weekly PFB/ME regimen resulted in > 50% clinical CR for patients with very advanced oral carcinoma. If patients can accept planned surgery with or without adjuvant radiotherapy, improvement in local control and survival with low or no radiation morbidity can be predicted. In our personal view and from clinical experience, resection of the original tumor bed area and good reconstruction after neoadjuvant chemotherapy will produce the greatest chance of durable local control and highest functional results when compared with concomitant chemoradiotherapy alone and sequential chemotherapy plus radiotherapy. Some oncologists favor organ preservation and avoidance of destructive surgery. This approach has been proven useful for laryngeal and hypopharyngeal carcinomas, but not for other head and neck carcinomas.[12,23] Our data show that omitting surgery will sacrifice tumor control in patients with advanced oral carcinoma. Weekly PFB/ME is a highly effective neoadjuvant chemotherapy regimen with low toxicity for oral carcinoma. However, implementing the integration of this regimen into a multimodality therapy protocol requires further study.

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