Phase II trial of biweekly gemcitabine and paclitaxel with recurrent or metastatic squamous cell carcinoma of the head and neck: Southwest Oncology Group study S0329

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ABSTRACT: *Background.* A phase I study and an institutional pilot study in patients with metastatic/recurrent squamous cell carcinoma of the head and neck (SCCHN) utilizing biweekly gemcitabine and paclitaxel (GEMTAX), showed an overall response rate of 53%. 1 This phase II trial was conducted to determine the feasibility, tolerability, and efficacy of this combination.

Methods. Patients with metastatic/recurrent SCCHN were treated with gemcitabine (3000 mg/m2) and paclitaxel (150 mg/m2) on days 1 and 15 of every 28-day cycle.

Results. In 57 patients with measurable disease, median progression-free survival (PFS) was 4 months and median overall survival (OS) was 8 months. Overall response rate of 28% and disease stabilization in 19% were seen. There were no treatment-related deaths with grade 3/4 hematologic toxicity seen in 20% of the patients.

Conclusion. Biweekly GEMTAX is feasible, well tolerated, and demonstrated reasonable efficacy. This may be an alternative for patients who are not candidates for platinum-based chemotherapy. © 2014 Wiley Periodicals, Inc. *Head Neck* **36:** 1712–1717, 2014

KEY WORDS: gemcitabine, paclitaxel, recurrent, metastatic, squamous cell carcinoma of the head and neck

INTRODUCTION

Worldwide, 640,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) are diagnosed annually,[1] the majority presenting with locoregionally advanced disease. Patients with locally advanced SCCHN are at high risk for developing local and distant relapses. Those who develop metastatic disease or recurrent disease, which is not amenable to salvage surgery or reirradiation, have a dismal prognosis, and treatment generally consists of palliation with combination chemotherapy. Cisplatin in combination with 5-fluorouracil (5-FU) or paclitaxel is considered the standard of care, achieving response rates from 30% to 40%, with a median survival of 6 to 9 months.[2] Addition of the monoclonal antibody, cetuximab, with platinum and 5-FU prolongs the median survival to 10 months.[3] Newer agents and combination treatments are thus needed to improve the outcomes in this clinical setting.

Taxanes and gemcitabine are both active in SCCHN and are known to have different mechanisms of action with demonstrable single agent activity and non-overlapping toxicity profiles.[4–8] Most of the clinical experience with paclitaxel[4,5] has been with a once every 3-week drug administration schedule, whereas the majority of clinical experience with gemcitabine[6,8] has been with a schedule that administers the drug on a weekly basis, 3 of every 4 weeks or 2 of 3 weeks. However, phase I data for an every-other-week administration schedule has been published. In 2 separate studies, the maximum tolerated dose for gemcitabine was 3000 mg/m2[9] and 4560 mg/m2,[10] respectively. Gemcitabine and paclitaxel (GEMTAX) were subsequently used in combination in a phase I trial by Rothenberg et al[11] in 37 patients with solid tumors refractory to conventional therapy. Dose limiting toxicity was not seen at doses of 150 mg/m2 of paclitaxel and 3000 mg/m2 of gemcitabine biweekly and this dose and schedule of paclitaxel and gemcitabine was recommended for phase II evaluation.

Based on the data from this phase I study, a pilot study at Wayne State University utilizing a biweekly GEMTAX regimen was conducted. This study demonstrated a 53% objective response rate in patients with advanced or recurrent head and neck cancer who had failed prior chemotherapy.[12] Hence, a phase II trial with the same GEMTAX regimen was then conducted by the Southwest Oncology

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Group (SWOG) in an effort to establish the feasibility, efficacy, and toxicity of this novel regimen in a setting of patients with recurrent/persistent or metastatic SCCHN. Here, we report the results of this multi-institutional study.

MATERIALS AND METHODS

Eligibility

Patients with histologically proven SCCHN that was either metastatic or had persisted or recurred after definitive surgery and/or radiation therapy or chemoradiation were eligible. Prior chemotherapy for recurrent or metastatic disease was not permitted. Patients with prior induction or adjuvant therapy were eligible if at least 6 months had elapsed from their last course of chemotherapy. Prior treatment with gemcitabine or taxanes as part of induction, concurrent, or adjuvant therapy was not allowed and no more than 1 regimen of induction or adjuvant therapy was permitted. Prior radiation had to be completed at least 28 days before registration on this study with resolution of all toxicity from prior therapy. Patients with both measurable and nonmeasurable disease were permitted to enroll. All measurable disease had to be assessed within 28 days before registration, which was defined by using the Response Evaluation Criteria in Solid Tumors (RECIST).[13] All nonmeasurable disease had to be assessed within 42 days before registration. Participants were required to be at least 18 years of age, to have a Zubrod Performance Status ≤ 1 and without any $\geq$ grade 2 sensory neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0). Patients with any prior or active central nervous system metastasis, active infection requiring systemic therapy, or a history of hypersensitivity reaction to products containing polysorbate 80 were excluded. Adequate organ function documented by a serum creatinine <2 times institutional upper limit of normal (ULN), bilirubin ≤ 2 times institutional ULN, alkaline phosphatase <2 times institutional ULN or serum glutamic-pyruvic transaminase <2 times institutional ULN were prerequisites for study enrollment. Adequate cell counts as detailed by a granulocyte count $>1500/\mu l$ and a platelet count $>100{,}000/\mu l$ were required. Concomitant treatment with another modality, such as gene therapy, biologic therapy, etc., was not permitted while the patient was on study. Patients with significant comorbidities that might affect their ability to tolerate the treatment were excluded. No prior malignancies were allowed except for adequately treated basal cell (or squamous cell) carcinoma of the skin, in situ cervical cancer, or other cancers from which the patient had been disease-free for 5 years. Pregnant or nursing women could not participate in this trial and women/men of reproductive potential could participate only if they agreed to use an effective contraceptive method. The study was approved by the institutional review boards at each participating institution, and all patients provided informed consent.

Treatment plan

Gemcitabine (3000 mg/m2) was infused over 30 minutes on days 1 and 15 every 28 days. Paclitaxel (150 mg/m2) was infused after gemcitabine over 60 minutes on days 1 and 15 of every 28-day cycle. Every patient receiving paclitaxel was premedicated with dexamethasone 20 mg intravenously (IV), diphenhydramine 50 mg, and ranitidine 50 mg IV, 30 to 60 minutes before infusion. Serotonin antagonist was given IV or PO as clinically indicated. Each treatment cycle was repeated every 28 days if there was complete resolution of toxicity.

Treatment evaluations and dose modifications

Before enrollment, patients underwent a history and physical examination. Pretreatment laboratory studies included a complete blood cell count with differential and serum chemistries, including creatinine to monitor the renal function. National Cancer Institute Common Terminology Criteria for Adverse Events version 3 was used to classify the adverse effects. Dosage modifications were done based on the absolute neutrophil count (ANC) and platelet counts on the day of treatment. If the ANC was >1500 and platelets $>100{,}000$, then the full dose was administered. If the ANC was 1250 to 1500 and/or platelets were 85,000 to 100,000, the dose was decreased to 2250 mg/m2 of gemcitabine and 112.5 mg/m2 of paclitaxel. If the ANC was 1000 to 1249 and/or platelets were 70,000 to 85,000, the dose was decreased further to 1500 mg/m2 of gemcitabine and 75 mg/m2 of paclitaxel. If the ANC decreased to <1000 or platelets to $<70{,}000$, the dose was withheld. If the cell counts recovered within 1 to 3 weeks to an ANC >1500 and platelets $>100{,}000$, treatment was resumed at the reduced dose of 1500 mg/m2 of gemcitabine and 75 mg/m2 of paclitaxel; if hematologic recovery took more than 4 weeks, patients were taken off protocol. For grade 2 neurotoxicity, paclitaxel dose was reduced to 112.5 mg/m2, and for grade 3 toxicity, patients were removed from protocol.

Response assessment

All measurable lesions up to a maximum of 5 lesions per organ or 10 lesions representative of all involved organs were identified as target lesions at baseline. Measurements of the target lesions were used for assessing the objective response. Response was assessed after every 2 cycles (1 cycle = 28 days). If patients went off treatment before disease progression, then disease assessments continued every 8 weeks until progression was documented. Objective status was recorded at each evaluation and response was evaluated according to the RECIST criteria. Patients who achieved a complete response were removed from treatment after they received 4 additional cycles of chemotherapy. Otherwise, patients were treated until disease progression, symptomatic deterioration, or unacceptable toxicity. Patients with nonmeasurable disease were not included in the response assessment.

Statistical considerations

The main purpose of this study was to assess overall survival (OS) in patients with advanced or recurrent SCCHN when treated with gemcitabine plus paclitaxel on a biweekly schedule. The regimen would be considered unpromising if the true median survival were ≤ 6 months. With 65 patients accrued over 12 months, and an additional 12 months of follow-up, the power of a 1-sided 0.05 exponential score test would be 0.90. If the observed median survival was ≥ 7.5 months, the regimen was to be considered for further study.

Secondary objectives of this study were to assess progression-free survival (PFS), to assess response in the subset of patients with measurable disease, and toxicity. Sixty-five patients were considered sufficient to estimate the median PFS within ±12% (95% confidence interval [CI]). If 55 patients had measurable disease, the probability of response could be estimated within ±13% (95% CI). Sixty-five patients were sufficient to estimate the probability of any specific adverse event to within ±12% (95% CI). Any adverse event occurring with at least 5% probability was likely to be seen once (96% chance).

All eligible patients who received at least 1 dose of the study drug were analyzed for efficacy and toxicity endpoints. Continuous variables are presented using median (range). Categorical variables are summarized in frequency tables. OS and PFS estimates were calculated using the method of Kaplan–Meier.[14] The 95% CI for the median OS and PFS were constructed using the Brookmeyer and Crowley method.[15] The 95% CI for point estimates were constructed using the log-log transformation.

The response rate was defined as the number of patients with complete or partial responses among the subset of patients with measurable disease (per RECIST) at baseline. Exact binomial CIs were calculated for response outcomes. All analyses were performed using SAS version 9.2.

RESULTS

Patient characteristics

Sixty-seven patients were accrued between January 1, 2005, and January 1, 2007, from 19 participating institutions. Three patients were ineligible, 2 patients who had received prior systemic chemotherapy for their recurrent or newly diagnosed disease, and 1 patient who had newly diagnosed disease that was not metastatic. In addition, 1 eligible patient did not receive any protocol treatment because of deteriorating performance status. This patient was not analyzable for any of the study endpoints. Thus, 63 patients were evaluable. There was an expected male predominance with a median age of 63 years (range, 40–82 years). The most commonly involved primary sites included the oral cavity (32%), oropharynx (21%), and larynx (25%). At baseline, 57 patients had at least 1 measurable lesion and 6 patients had only nonmeasurable disease. Among the 63 evaluable patients, 25% of the patients had a locoregional recurrence/progression, 34% had a distant metastatic involvement, and 41% had a combined locoregional and metastatic involvement. Patient characteristics are detailed below in Tables 1 and 2.

Toxicities

All 63 patients were evaluated for toxicities. There were no treatment-related deaths. Nine patients (14%) experienced grade 4 treatment-related adverse events, which were primarily hematologic, but also included 1 case each of thrombosis/embolism, fatigue, and dyspnea. Twenty-four additional patients (38%) experienced grade 3 treatment-related adverse events. All grade 3 and 4 adverse events are reported in Tables 3 and 4.

TABLE 1. Patient characteristics.

Characteristic	No. of patients (%)
Age	
Median (range), y 63 (40–82)	
Sex	
Male	50 (79)
Female	13 (21)
Race	
White	50 (79)
Black	11 (17)
Multiracial	1 (2)
Unknown	1 (2)
Performance status	
0	24 (38)
1	39 (62)
Disease status	
Newly diagnosed	5 (8)
Persistent	7 (11)
Recurrent	50 (79)
Not reported	1 (2)
Primary site*	
Lip/oral cavity	20 (32)
Nasopharynx	4 (6)
Oropharynx	13 (21)
Salivary glands	0
Hypopharynx	2 (3)
Larynx	16 (25)
Paranasal sinuses	3 (5)
Other/unknown	5 (8)

* Human papillomavirus status was not tested.

Treatment and tolerance

The median number of cycles administered per patient was 3 (range, 1–14). Eight patients (13%) received just 1 cycle and 52 patients (83%) received between 2 and 6 cycles. Three patients (5%) received 6 cycles of treatment and another 15 patients (24%) received 4 or more cycles of treatment. Twenty-nine patients (46%) required dose reductions during chemotherapy. Three patients were taken off the protocol for worsening neuropathy and another 2 patients discontinued treatment for worsening performance status despite stable disease in 1 patient and a partial response in the other.

Response to treatment

The 57 patients who had measurable disease at baseline were evaluable for response. Complete response was seen

TABLE 2. Patient characteristics: prior treatments.

Prior treatments	No. of patients (%)
No prior therapy	8 (12)
Radiation therapy	9 (14)
Surgery	5 (8)
Surgery, radiation therapy	17 (26)
Radiation, concurrent chemotherapy	12 (18)
Surgery, radiation therapy, concurrent chemotherapy	9 (14)
Surgery, radiation therapy, multiagent chemotherapy	1 (2)
Multiagent systemic chemotherapy	1 (2)
Radiation therapy, multiagent systemic therapy	4 (6)

TABLE 3. Hematologic adverse events possibly, probably, or definitely related to treatment.

Adverse event	No. of patients	
	Grade 4 (%)	Grade 3 (%)
Anemia	1 (2)	1 (2)
Leukocytopenia	1 (2)	1 (2)
Neutropenia	4 (6)	3 (5)
Lymphopenia	0	3 (5)
Thrombocytopenia	2 (3)	0
Maximum grade any hematologic adverse event	6 (10)	6 (10)

in 2 patients (3%), 1 of which was unconfirmed. An additional 14 patients (25%) had a partial response, including 6 confirmed and 8 unconfirmed. The estimated response rate (confirmed + unconfirmed complete and partial responses) was 28% (95% CI, 17% to 42%). A best response of stable disease was noted in 11 patients (19%); hence, the estimated disease control rate was 47% (95% CI, 34% to 61%). Progressive disease was seen in 21 patients (37%). The remaining 9 patients could not have their exact response determined because of inadequate assessments.

PFS and OS, are illustrated in Figures 1 and 2 below. The estimated median PFS was 4 months (95% CI, 3–6 months). The estimated median OS was 8 months (95% CI, 7–11 months) and the estimate of 1-year survival was 37% (95% CI, 25% to 48%).

TABLE 4. Nonhematologic adverse events possibly, probably, or definitely related to treatment.

Adverse event	No. of patients	
	Grade 4 (%)	Grade 3 (%)
Acne	0	1 (2)
Allergic reaction	0	1 (2)
Anorexia	0	1 (2)
Dehydration	0	1 (2)
Diarrhea	0	2 (3)
Dyspnea	1 (2)	1 (2)
Fatigue	1 (2)	7 (11)
Febrile neutropenia	1 (2)	2 (3)
Hyperglycemia	0	1 (2)
Hyponatremia	0	3 (5)
Hypotension	0	1 (2)
Infection, 0–2 ANC: catheter-related	0	1 (2)
Lung hemorrhage: nose	0	1 (2)
Lung infection, 0–2 ANC: lung	0	1 (2)
Lung infection, 3–4 ANC: lung	0	1 (2)
Memory impairment	0	1 (2)
Mucositis, function: oral cavity	0	1 (2)
Muscle weakness: whole body	0	1 (2)
Musculoskeletal pain: bone	0	1 (2)
Neuropathy-motor	0	1 (2)
Neuropathy-sensory	0	3 (5)
Pain-other	0	1 (2)
Pneumonitis	0	1 (2)
Rash	0	1 (2)
Thrombosis/embolism	1 (2)	0
Vomiting	0	1
Maximum grade any nonhematologic adverse event	4 (6)	22 (35)

Abbreviations: ANC, absolute neutrophil count.

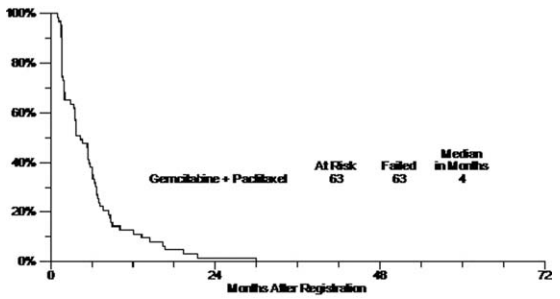

FIGURE 1. Progression-free survival.

DISCUSSION

In this open label multicenter phase II study, first-line treatment with the biweekly regimen of GEMTAX in patients with recurrent or metastatic disease was noted to be feasible, tolerable, and effective. Median PFS was noted to be 4 months and median OS was 8 months in this phase II study. As per the study protocol, an OS of >7.5 months was considered to be worthy of further evaluation. Of the 57 evaluable patients, 16 patients demonstrated a response and disease stability was seen in another 11 patients totaling a 47% disease control rate. The OS seen with this regimen is comparable to the prior experience with platinum-based combination chemotherapy regimens that demonstrate OS rates of 6 to 9 months across studies.[2,3] This observation is especially important as this provides an option for patients who are not candidates for treatment with platinum-based regimens for various reasons, such as poor renal function, hearing loss, or hypersensitivity. Even though this study did not assess refractoriness to platinum compounds before enrollment, the results of this study do open an avenue for patients who might be ineligible for or refractory to platinum-based therapy. Hence, GEMTAX may serve as a reasonable alternative in these select populations.

Although the survival rates are comparable to other combination regimens, response rates reported in this study were somewhat lower than expected, 28% versus 30% to 40% reported with most doublets. This may be because of the refractory nature of the disease being studied, as most patients had previously treated recurrent

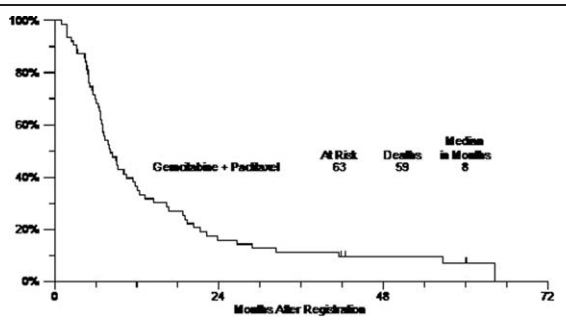

FIGURE 2. Overall survival.

disease and only 5 patients had a new diagnosis of metastatic disease without prior therapy. Also, of 57 evaluable patients, 9 patients with an inadequate assessment of response were included for intent-to-treat analysis (accounting toward the denominator — total number "N") which may account for the modest response rate. Seventy-eight percent of the patients in this study had received prior treatment with radiation therapy and 79% of the patients had a primary tumor site other than the oropharynx. In general, chemotherapy does not work as well in patients who have undergone prior treatment with radiation. In a study by Argiris et al,[16] oral cavity and hypopharyngeal primary tumors (accounting for over 50% of the patients studied in our trial) and prior radiation were noted to be independent unfavorable predictors of objective response, as was an Eastern Cooperative Oncology Group performance status of 1 (vs 0). Sixty-two percent of the patients in this SWOG experience had a performance status of 1.

Both paclitaxel and gemcitabine are active and well tolerated in patients with SCCHN, without any pharmacokinetic or pharmacodynamic interactions that may interfere with the efficacy of these drugs.[7] The gemcitabine dose of 3000 mg/m2 was chosen based on the reported phase I and II data in a similar patient population[12] and was tolerated relatively well. The combination of gemcitabine and paclitaxel in this study was not associated with any treatment-related deaths. Grade 3 and 4 neutropenia was seen in only 11% of the patients and thrombocytopenia in 3%, which is much less than the rate of hematologic toxicity seen with the contemporary platinum-based regimens[2,3,17] and comparable to some of the novel combinations being studied.[18] Although 29 patients (46%) required dose reductions, only 5 patients had to stop treatment because of nonhematologic toxicity. Tolerability of this high dose of gemcitabine was also demonstrated in another phase II study by Kafri et al,[19] in which 76% of the patients completed treatment without dose reductions. These findings are also significant as treatment options for patients with head and neck cancer are often limited by secondary to multiple comorbidities and declines in performance status from previous therapies. Although GEMTAX was used only as front-line therapy in this study, this combination of gemcitabine and paclitaxel might be a reasonable second-line treatment strategy. Further studies are needed, however, to prove this hypothesis.

A prior phase I/II study with gemcitabine (800 mg/m2 on days 1 and 8, increased to 1000 mg) with escalating doses of paclitaxel resulted in an overall response rate of just 14.8% and median survival of 24 weeks.[20] In our study, we used the same drugs but with a higher dose of gemcitabine and a dosing interval of every 2 weeks, which may have accounted for improved efficacy. The every 2 week dosing interval allowed for complete hematologic recovery and may have facilitated the administration of high doses without prohibitive cytopenias.

More recently, we have seen an improvement in the median OS from 7.4 to 10 months when cetuximab was added to platinum and 5-FU for treatment of patients with cancers of the head and neck. Although this has been a landmark breakthrough, this strategy involves use of a third drug, weekly infusions, and continued maintenance cetuximab in patients with stable disease. This raises the question of whether maintenance therapy is better than sequential second-line therapy, a question that remains to be answered, and whether the additional cost of cetuximab is justified.[3] Another recent phase II study by Argiris et al[18] evaluating a combination of pemetrexed and bevacizumab demonstrated a median OS of 11 months, which is very encouraging; however, half the patients in this study had an oropharyngeal primary, suggesting a large proportion of human papillomavirus (HPV)-related disease that would have responded well with many conventional therapies.

Finally, when the responses in our study were evaluated according to the primary site involved, there was a trend toward better response in patients with an oropharyngeal primary. Of the 12 patients with measurable disease, 6 patients had a response (2 documented complete responses and 4 partial responses), another 3 patients had stable disease, 2 patients had inadequate assessments, and 1 patient had progressive disease on treatment. This was not a preplanned subgroup analysis and the number of patients is small but the findings are concordant with the published literature if not better, with a disease control rate of at least 75%.[16] HPV status was not available in our patients, hence, we can only hypothesize that HPV positivity may have accounted for better outcomes seen in this subgroup.

In conclusion, this multicenter, phase II study confirms the feasibility, tolerability, and efficacy of a biweekly regimen of gemcitabine and paclitaxel. The favorable results, seen in a recurrent population with mainly nonoropharyngeal primary tumors, are relevant, suggesting that GEMTAX is worthy of further study. Although the median survival of 8 months seems modest in the current context of multi-drug combination and directed therapies, it is definitely comparable to other chemotherapy combinations with respect to survival and responses. There may be limitations to pursuing a phase III study with this combination, but knowledge of its activity in a population with poor prognostic risk factors is very pertinent to clinical practice.

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