

Biweekly gemcitabine and paclitaxel in patients with relapsed or metastatic squamous cell carcinoma of the head and neck

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ABSTRACT

Purpose: We conducted a Phase II, clinical trial to evaluate the efficacy and safety of a biweekly gemcitabine and paclitaxel (GEMTAX) regimen as second-line treatment in patients with recurrent or metastatic unresectable, squamous cell carcinoma of the head and neck (SCCHN). The primary endpoint was response rate. **Patients and Methods:** Patients with recurrent unresectable or metastatic platinum refractory SCCHN, who had performance status ≤ 2 and adequate organ function, were eligible. Gemcitabine (3000 mg/m² intravenous) and paclitaxel (150 mg/m² intravenous) was given on days 1 and 15 of 4 weeks cycle, until patients had disease progression or unacceptable toxicity. **Results:** Disease control (partial response [PR] + complete response [CR] + stable disease [SD]) was noted in 19 patients (54%) and overall response (CR + PR) was noted in 8 patients (23%). However, the most frequent response outcomes were progressive disease in 16 patients (46%) and SD in 11 patients (31%). The most frequent Grade 3–4 adverse events were lymphopenia in 38 patients (75%), anemia in 20 patients (39%), and infection in 16 patients (31%). Median progression-free survival was 3.6 months; median overall survival was 6.3 months. **Conclusion:** The biweekly GEMTAX regimen has statistically significant grade 3 and 4 adverse events and has meaningful clinical activity as a second-line treatment in patients with recurrent or metastatic SCCHN who have received prior chemotherapy. This regimen may particularly be a useful treatment option in patients who progressed in less than 6 months months of concurrent chemoradiotherapy with high-dose cisplatin and/or have recurrent/metastatic platinum refractory SCCHN.

Key words: Gemcitabine, head and neck cancer, paclitaxel

INTRODUCTION

Head and neck cancer are the sixth most common neoplasm worldwide with nearly 560,000 new cases reported each year.^[1] Approximately, 95% of these tumors are squamous cell carcinoma of the head and neck (SCCHN) arising primarily from the lip/oral cavity, oropharynx, hypopharynx, and larynx. Other less common cancers include mucoepidermoid carcinomas, adenoid cystic carcinomas, and adenocarcinomas, originating from the

salivary glands. The main types of treatment failure are loco-regional recurrences and metastatic disease.^[2]

Patients, with early (Stage I and II) disease, usually are treated with surgery or radiation therapy. Effective approaches for locally advanced SCCHN include primary surgery followed by either postoperative radiotherapy with or without concurrent chemotherapy or definitive concurrent chemoradiotherapy. Most patients with recurrent SCCHN after definitive surgical or nonsurgical treatments have a

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poor prognosis, with a median overall survival (OS) of 6–9 months.^[3]

Chemotherapy is the main treatment modality for patient with recurrent unresectable or metastatic head and neck squamous-cell carcinoma (SCCHN).^[4] Several studies have shown improvement in quality of life in addition to OS and progression free survival (PFS) advantages using platinum containing regimens as a first-line palliative chemotherapy option.^[4,5]

Treatment options for relapsed unresectable or metastatic (R/M) SCCHN are limited, depending on previous treatments received. Standard first-line treatment of R/M SCCHN is platinum-based chemotherapy. Nonetheless, once patients progress on platinum-based chemotherapy, therapeutic options are limited, and most patients would receive only best supportive care.^[6]

Vermorken and Specenier^[7] reviewed different trials that examined the efficacy of several single agents in patients with recurrent or metastatic SCCHN. Paclitaxel was among the most effective agents, with response rates varying between 20% and 43%.^[7] In a Phase II clinical trial of weekly paclitaxel in platinum resistant Stage IV SCCHN, 43% disease control was observed.^[8]

Gemcitabine is a synthetic pyrimidine antimetabolite that interferes with DNA synthesis by inhibiting ribonucleotide reductase, competing with deoxycytidine triphosphate, and halting DNA polymerization.^[9] Paclitaxel acts at the transition from the G2 phase to mitosis, inducing cell blockage.^[10] Both gemcitabine and paclitaxel (GEMTAX) have a radiosensitizing effect in SCCHN.^[11-14] Gemcitabine has been reported to have antitumor activity with 38% response rate in advanced SCCHN.^[15]

In previously treated recurrent or metastatic SCCHN, the combination of gemcitabine and docetaxel (GEMDOC) resulted in disease control in 55% of the patients enrolled in 55% of patients, with median OS of 4.2 months.^[16] Others have reported similar results with biweekly GEMDOC in nonsmall cell lung cancer.^[17,18] Hellenic Cooperative Oncology Group report a response rate of 20% for GEMTAX in advanced nonnasopharyngeal head and neck cancer, where paclitaxel was given at 175 mg/m² on day 1 and gemcitabine at 1000 mg/m² on days 1 and 8 every 3 weeks.^[19] Rothenberg *et al.* defined the maximum tolerated dose of the combination of gemcitabine 3000 mg/m² and paclitaxel 150 mg/m² (GEMTAX).^[20] Due to the lack of a standard treatment for platinum refractory R/M SCCHN, we conducted this Phase II clinical multi-staged clinical trial

to assess the efficacy of GEMTAX regimen in the treatment of R/M HNSCC.

PATIENTS AND METHODS

Patients selection

Patients with histologically proven R/M HNSCC, who progressed after receiving platinum based definitive concurrent chemo-radiation therapy or first-line palliative chemotherapy with, single agent platinum or methotrexate, or combination of platinum and 5-fluorouracil, were eligible. Prior radiation or chemotherapy must have been completed 4 weeks before enrolment. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS)^[21] of ≤ 2 and a life expectancy of ≥ 12 weeks. All patients had to have (absolute neutrophil count [ANC], $\geq 1.5 \times 10^9/L$; platelet [PLT] count, $\geq 100 \times 10^9/L$), (total bilirubin, alkaline phosphatase and serum glutamic-oxaloacetic transaminase (SGOT) < 2 times the institutional upper normal) and adequate renal functions (creatinine 2 mg/dL). Patients were excluded if they had a history of prior therapy with gemcitabine or paclitaxel, any therapy during the 4 weeks before enrollment, or central nervous system metastases. Pregnant or nursing women were not allowed to participate. Women and men of reproductive age must have agreed to use an effective contraceptive method. The institutional review board of Wayne State University approved the study, and all patients provided signed informed consent.

Study design

The primary objective of this trial was to evaluate response rate. Secondary objectives were OS, PFS and the toxicity profile of biweekly GEMTAX regimen in this patient population.

Patients were given gemcitabine (3000 mg/m² intravenous over 30 min) followed by paclitaxel (150 mg/m² intravenous over 60 min). This treatment was given on days 1 and 15 of each 28-day cycle. The treatment was given until disease progression, unacceptable toxicity, holding treatment secondary to hematological toxicity (3 consecutive weeks) or nonhematological toxicity (4 week), the patient's request to withdraw from the study, recommendation by the physician to stop the treatment, or complete remission plus four cycles, whichever occurred first.

All patients who received chemotherapy or any portion of a cycle of therapy were evaluated for toxicity every 2 weeks. Toxicity was graded according to CTCAE version 3.0 (National Cancer Institute, Bethesda, MD, USA).^[22] Serious adverse events included Grade 3–4 hematologic and

nonhematologic toxicities. Concurrent illnesses, infections, blood product support, and antimicrobial therapies were monitored.

Dose was modified according to the severity of the adverse events whether they were hematological, non-hematological or neurological. Dose modifications for hematological toxicities were at four levels requiring adjustment of both drugs together; the first level when neutrophils (ANC) >1500 and PLT >100,000, patients were given 100% of the dose, the second level when ANC = 1250–1500 and PLT = 85,000–100,000, patients were given 75% of the dose, the third level when ANC = 1000–1.249 PLT = 70,000–84,999, patients were given 50% of the dose, the fourth level when ANC was <1000 or PLT <70,000 patients were given 0% of the dose. If the treatment was held, it was resumed within 1–3 weeks if the count recovered to the first level values. If the recovery extended beyond four weeks, patients were taken off the treatment. For Grade 2 and 3 neurotoxicity, paclitaxel was reduced by 25% and 50% respectively. Patients were taken off the treatment if Grade 3 neurotoxicity persisted. Other Grade 3 or 4 toxicities required 25% and 50% dose reduction respectively, resuming the following treatment if the toxicity recovers to Grade 2 or less. Patients were taken off the treatment and the delay was more than 4 weeks

Assessment

Patients were evaluated before each treatment (2 weeks) by obtaining history, physical exam, complete blood count, creatinine, electrolytes, alkaline phosphatase, SGOT, total bilirubin, albumin at baseline then every 2 weeks. Upon baseline imaging, patients were assigned into; evaluable measurable disease (bi-dimensionally measurable lesion), and evaluable nonmeasurable (uni-dimensionally measurable lesion). Tumor response was assessed radiographically using Response Evaluation Criteria in Solid Tumors (RECIST) at baseline then every 8 weeks (2 cycles).^[23] The RECIST ratings were progressive disease (PD), SD, PR, or CR.^[23] The overall response frequency (OR) was defined as the sum of patients who had PR or CR; disease control (DC) frequency was defined as the sum of patients who had SD, PR, or CR. Patients with nonevaluable disease were not assessed for response rate.

Statistical methods

This single-institution Phase II trial was planned with a Fleming two-stage design.^[24]

The primary endpoint was response rate (CR + PR). We wished to distinguish these regions of the true, unknown response rate: At most 0.05 versus at least 0.20. A true response rate of ≤ 0.05 would indicate that the regimen

was not worthy of further study in this patient population. However, a true response rate of ≥ 0.20 would be promising. The two-stage design called for a maximum of 40 response evaluable (r-e) patients, 20 in Stage 1 and 20 in Stage 2. The design had a Type I error of 0.052 and power of 0.922. At the interim analysis (i.e. among the first 20 r-e patients), if there were 1–3 responders, accrual should continue. The best OR was the best response recorded from the start of treatment until disease progression. The duration of response (PR or CR) was the time from the best response until the first date recurrence or PD was recorded. Duration of SD was the time from the start of treatment until the onset of PD.

For response and toxicity rates, Wilson type 95% confidence intervals (CIs) were calculated. Response duration (RD) was measured from the start of the best response until relapse. Patients still in remission were censored as of the date of their last tumor assessment. Due to the small number of responders, 80% confidence level was used for the CI of RD. Time to treatment failure (TTF) was measured from registration until early discontinuation of treatment, first observation of PD, or death from any cause, whichever occurred first. Patients still on treatment were censored as of the date of their last tumor assessment. PFS was measured from registration until the date of documented PD or death from any cause, whichever occurred first. Patients still alive and progression-free were censored as of the date of their last tumor assessment. OS was measured from registration to the date of death from any cause. Patients still alive were censored as of the most recent date on which they were known to be alive. Standard KaplanMeier estimates of the censored RD, TTF, PFS, and OS distributions were computed. Due to the small sample sizes, survival statistics (e.g. median, 6-month rate, etc.) were estimated more conservatively using linear interpolation among successive event times on the Kaplan-Meier curves.^[25]

RESULTS

Patients characteristics

Fifty-five eligible patients were enrolled; 51 patients received treatment on trial; 43 (78%) males and 31 (56%) white. The primary types of SCCHN were 22 (40%) oropharyngeal carcinoma, 13 (24%) oral cavity, and 11 (20%) laryngeal. Majority of the patients that is, 46 patients (98%), had ECOG PS of 0 or 1 [Table 1].^[21] Regarding previous treatment for SCCHN, all patients had prior radiation therapy, and 81% had prior surgery. Regarding prior systemic treatment, four patients received only one prior line of treatment as adjuvant or palliative first line chemotherapy and 51 patients received two lines of treatment (one as adjuvant and one as palliative

chemotherapy) [Table 1].

Toxicities

Fifty-one treated patients were assessed for adverse events. Grade 3–4 hematological toxicities included leukopenia in 10 (20%) patients, neutropenia in 8 (16%) patients, lymphopenia in 38 (75%), anemia in 20 (39%), and thrombocytopenia in 1 (2%) of the patients [Table 2]. The most frequent Grade 3–4 nonhematologic toxicity was infection. Nonhematological Grade 3–4 toxicities included infection in 16 (31%), fatigue

in 2 (4%), vomiting in 1 (2%), dyspnea in 1 (2%) and others in 1 (2%) of the patients. Neuropathy occurred as Grade 1 and 2 in 11 and 5 patients respectively [Table 3].

Response, progression free survival, and overall survival

Among the 35 response-evaluable patients; 11 (31%) patients had SD, 5 (14%) patients had PR, 3 (9%) patients had CR, with DC was noted in 19 patients (54%) and OR was noted in 8 patients (23%; 95% CI: 12–39%). To conclude that the treatment regimen was promising required observing at least 5 responders. With 8 responders, it was concluded that the regimen was promising and that the sample response rate among the response evaluable patients (8/35 = 23%) supported the alternative hypothesis [Table 4].

Median PFS was 3.6 months (95% CI: 2.5–4.4 months), and 6 months PFS was 22% (95% CI: 9–36%) [Figure 1]. Median OS was 6.3 months (95% CI: 4.1–7.7 months), 6 months survival was 51% (95% CI: 38–64%) and one-year survival

Table 1: Demographic and clinical characteristics*

Characteristic	Median (range) or number (%)
Age (year)	56 (23-84)
Sex	
Male	43 (78)
Female	12 (22)
Race	
White	31 (56)
African American	24 (44)
ECOG performance status [†]	
0	13 (28)
1	33 (70)
2	1 (2)
Previous treatment	
Radiation therapy	55 (100)
Surgery [‡]	43 (81)
Previous chemotherapy	
Adjuvant or first-line relapse	51 (93)
Adjuvant and first-line relapse	4 (7)
Primary site of disease	
Oropharyngeal	22 (40)
Oral cavity	13 (24)
Laryngeal	11 (20)
Hypopharyngeal	7 (13)
Other	2 (4)
Extent of disease [§]	
Local/regional	15 (28)
Metastases	38 (72)
Lung metastasis	24 (44)
Treatment cycles [§]	2.5 (0-10)

*Before treatment with gemcitabine and paclitaxel, n=55 patients. Data reported as median (range, minimum to maximum) or number (%) patients. [†]ECOG: Eastern Cooperative Oncology Group, n=47 patients; data not available for eight patients. [‡]Surgery, n=53 patients; data not available for two patients. [§]Extent of disease, n=53 patients; data not available in two patients. [§]Gemcitabine and paclitaxel in current study

Table 2: Hematologic toxicity (n=51 treated patients)*

Type of hematologic toxicity	Worst grade					Grade 3-4 rate (%)	95% confidence limits (%)	
	0	1	2	3	4		Lower	Upper
Lymphopenia	4	1	8	26	12	38 (75)	61	84
Anemia	1	6	24	19	1	20 (39)	27	53
WBC	22	9	10	8	2	10 (20)	11	32
Neutropenia	36	4	3	7	1	8 (16)	8	28
Thrombocytopenia	40	7	3	1	0	1 (2)	0	10
Febrile neutropenia	0	0	0	0	0	0 (0)	0	7

*Data reported as number (%) (95% CI, minimum% to maximum%). Toxicity data were available in 51 patients (not available in 3 patients, and treatment was not given in 1 patient) WBC: White blood cell

Table 3: Nonhematologic toxicity (n=51 treated patients)*

Type of hematologic toxicity	Worst grade					Grade 3-4 rate (%)	95% confidence limits (%)	
	0	1	2	3	4		Lower	Upper
Infection	34	0	1	15	1	16 (31)	20	45
Fatigue	38	7	4	1	1	2 (4)	1	13
Vomiting	44	5	1	1	0	1 (2)	0	10
Dyspnea	49	1	0	1	0	1 (2)	0	10
Other nonhematologic toxicity	50	0	0	1	0	1 (2)	0	10
Peripheral neuropathy	35	11	5	0	0	0 (0)	0	7
Alopecia	42	4	5	0	0	0 (0)	0	7
Nausea	42	6	3	0	0	0 (0)	0	7

*Data reported as number (%) (95% CI, minimum% to maximum%). Toxicity data were available in 51 patients (not available in 3 patients, and treatment was not given in 1 patient). [†]Adverse event grade according to Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0, Bethesda, MD, USA: National Cancer Institute; 2006.^[22] [‡]Sum of number of patients who had Grade 3 or 4 toxicity. [§]No patients had febrile neutropenia or other hematologic toxicity. CI: Confidence interval

Table 4: Clinical response to treatment*

Response type [†]	Number of patients	Rate among 35 patients evaluated for response [‡]	Rate among all 55 registered patients [§]
Response evaluable patients	35		
SD	11	31 (19-48)	20 (12-32)
PR	5	14 (6-29)	9 (4-20)
CR	3	9 (3-22)	5 (2-15)
OR (PR + CR)	8	23 (12-39)	15 (8-26)
PD	16	46 (30-62)	29 (19-42)

*Response rate reported as percentage (%) (95% CI, minimum% to maximum%). [†]Response type: Response Evaluation Criteria in Solid Tumors. [‡]Patients evaluated for response, n=35 patients. [§]All patients, n=55 patients. SD: Stable disease, PR: Partial response, CR: Complete response, PD: Progressive disease, CI: Confidence interval, OR: Overall response

was 19% (95% CI: 9–30%) [Figure 2 and Table 5].

DISCUSSION

Patients with advanced, recurrent or metastatic SCCHN who were treated with biweekly GEMTAX on this Phase II clinical trial had a meaningful clinical benefit, with 54% DC rate (SD, PR, or CR) [Table 4]. Our group published a similar Phase II study using biweekly gemcitabine (3000 mg/m²) and docetaxel (60 mg/m²) with comparable DC rate.^[16] Median OS at (6.3 months; Table 3) was favorable in comparison to historical median OS data in this previously treated patient population.

The current combination of high dose GEMTAX caused considerable adverse events [Table 2], with mostly hematologic toxicities. In comparison to our previous GEMDOC study, GEMTAX resulted in similar rate of

Grade 3–4 anemia, lower rate of Grade 3–4 neutropenia and higher rate of Grade 3–4 infection [Table 2].^[16]

To the best of our knowledge, this is the first trial that used paclitaxel and gemcitabine at this dosage and schedule in this patient’s population. A Southwest Oncology Group (SWOG) study used the similar regimen with a different schedule to treat recurrent or metastatic SCCHN. However, that study was in patients who had no previous chemotherapy.^[19,26] Our study was conducted in patients who failed first-line chemotherapy. In the SWOG study, 57 patients were treated with a median PFS of 4 months and median OS of 8 months. Overall response rate was 28% and SD of 19%. There were no treatment-related deaths, and Grade 3/4 hematologic toxicity was seen only in 20% of the patients. The response rates of the SWOG study were similar to the present study, in spite of the difference in the inclusion criteria, where SWOG study was a first-line palliative chemotherapy in R/M SCCHN.

Table 5: Summary of statistics of TTE endpoints (n=55)*

TTE endpoint	n	Events	Point estimate %	95% CI	
Progression-free survival [†]	55	37			
Median			3.6 months	2.5 months	4.4 months
3 months rate			58	42%	73%
6 months rate			22	9%	36%
9 months rate			10	0%	21%
Overall survival	55	55			
Median			6.3 months	4.1 months	7.7 months
3 months rate			77	65%	88%
6 months rate			51	38%	64%
9 months rate			33	20%	45%
12 months rate			19	9%	30%

*n=55 patients. Data reported as median or (95% CI, minimum to maximum).

[†]Progression-free survival rate could not be determined at 12 months because last event was at 11 months. TTE: Time to event, CI: Confidence interval

On the other hand, this combination was tested in SCCHN with a different schedule before. Stier *et al.* report in Phase I-II trial with GEMTAX an OR rate of 14.8%. They concluded that the combination of paclitaxel and gemcitabine is tolerated but shows insufficient clinical activity in patients with recurrent and/or metastatic SCCHN to warrant further trials.^[27] However, biweekly GEMTAX has better efficacy and lower toxicity compared to the standard schedule of gemcitabine/paclitaxel, every 3 weeks. We have previously observed this regimen to be efficacious and well tolerated in patients with SCCHN^[26] and NSCLC.^[28]

The present study suggests that the biweekly GEMTAX

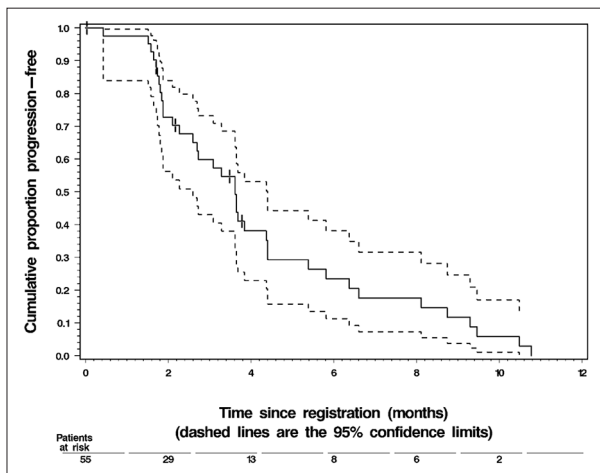


Figure 1: Kaplan–Meier plot of progression-free survival in patients who had squamous cell head and neck cancer and were treated with gemcitabine and paclitaxel (n = 55 patients)

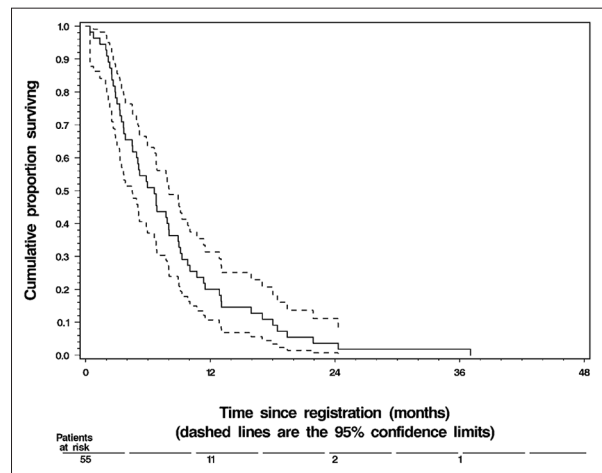


Figure 2: Kaplan–Meier plot of overall survival in patients who had squamous cell head and neck cancer and were treated with gemcitabine and paclitaxel (n = 55 patients)

regimen is feasible and effective.

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