

Gemcitabine and Cisplatin in Patients With Locally Advanced, Recurrent, or Metastatic Head and Neck Cancer: Results of a Phase II Trial

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ABSTRACT

Objectives: Determine the response to concurrent administration of gemcitabine plus cisplatin in patients with metastatic or locally advanced recurrent squamous cell carcinoma of the head and neck (SCCHN).

Patients and Methods: Patients with metastatic or locally advanced SCCHN that is persistent or recurrent following definitive therapy, and who did not receive prior chemotherapy for recurrent or metastatic disease. Eligible patients were enrolled onto a phase II study of gemcitabine 750 mg/m² intravenously (IV) plus cisplatin 25 mg/m² IV on Days 1, 8, and 15 of a 28-day cycle.

Results: Nine patients (median age, 59 years; range, 38-75 years) were enrolled. All patients had received prior surgery and radiation therapy. None of the patients received prior chemotherapy. Among the 9 patients, only 2 responses were observed for an overall response rate of 22%. Severe Grade 3-4 hemato-

logic toxicity was limited to thrombocytopenia (Grade 3 thrombocytopenia, 22%); however, no bleeding events were seen. There were 2 cases of death while patients were on active treatment, with 1 death probably related to treatment. The median time to progression was 6 weeks (range, 4-21 weeks). The median survival was 18 weeks (range, 0-32 weeks).

Conclusion: Gemcitabine plus cisplatin combination chemotherapy has modest activity in the treatment of recurrent or metastatic SCCHN.

INTRODUCTION

Current options for recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) produce only limited responses of short duration with median survival of 4-6 months. A number of single agents have shown activity in metastatic SCCHN including methotrexate, bleomycin, 5FU, cisplatin, and paclitaxel.¹ Combination chemotherapy has produced higher response rates but no survival advantage over single agent chemotherapy.² Combination chemotherapy regimens include platinum and 5FU, platinum and

Table 1. Patients Characteristics (N = 9).

Characteristic	Number of Patients*
Median Age	59 (38-75)
Sex	
Males	7
Females	2
Race	
White	8
Performance status	
0-1	4
3	5
Primary site	
Oral cavity	4
Larynx	3
Hypopharynx	1
Parotid gland	1
Prior chemotherapy	0
Prior radiation therapy	9
Recurrent (locally advanced)	3
Metastatic	6

*Unless otherwise indicated.

taxanes, and bleomycin- and mitomycin-containing combinations, among others.³

Gemcitabine (GEM) is a deoxycytidine nucleoside analog that requires intracellular phosphorylation of the parent drug to yields the active di- and triphosphate metabolites.⁴ The diphosphate form inhibits ribonucleotide reductase (an enzyme important for DNA biosynthesis), whereas the triphosphate form is incorporated into DNA, in competition with the normal nucleotide base deoxycytidine. This leads to termination of DNA chain synthesis.⁵ Cisplatin (CDDP) acts as an alkylating agent that binds to DNA, forming DNA adducts and thus inhibiting DNA synthesis.

The combination of DNA synthesis termination by GEM and CDDP through different mechanisms may lead to a synergistic effect of these 2 agents in vivo. Also, the difference in toxicity profile between the 2 agents makes the combination a good candidate for an

effective and well-tolerated combination chemotherapy regimen.

In vitro studies proved synergy between GEM and CDDP and suggested that interaction of GEM and CDDP was schedule-dependent with synergism observed when GEM is followed by CDDP.⁶ This combination has been studied in a nude mouse model with HNX-22B SCCHN cell line, and the combination was shown to be more active compared to either agent alone with at least additive benefit suggested.⁷ Several studies utilizing the combination of gemcitabine and cisplatin have been investigated in the treatment of advanced solid tumors, and it was shown to be safe with neutropenia as the major toxicity noted.⁸

We conducted a phase II study to determine the clinical activity of CDDP plus GEM in patients with metastatic or recurrent SCCHN when disease was not amenable to resection for cure.

PATIENTS AND METHODS

Eligibility

Patients with histologically confirmed SCCHN that is locally advanced, recurrent, or metastatic, with measurable unresectable disease, and who had not received previous chemotherapy regimens for treatment of recurrent or metastatic disease were eligible for participation on this study. Eligible patients must have had adequate organ function (defined as absolute neutrophil count [ANC] $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, total bilirubin ≤ 1.5 mg/dL, and serum creatinine ≤ 2.0 mg/dL) and Karnofsky performance status $\geq 50\%$. Patients must have completed any previous chemotherapy at least 4 weeks before enrollment, and they must have completed any previous radiation at least 4 weeks before enrollment. Those with measurable disease only within a previous radiation therapy port must have demonstrated clear evidence of progression prior to study entry.

Table 2. Treatment Response (N = 9).

Best Response	Number of Patients (%)
Complete response	0 (0%)
Partial response	1 (11%)
Minor response (SD)	1 (11%)
Non-evaluable	2 (22%)
Progressive disease	5 (55%)
Overall response rate	2 (22%)

Exclusion criteria included pregnant or lactating women and patients with active uncontrolled infection, or history of prior malignancy diagnosed within the past 5 years before enrollment. All patients provided written informed consent. The protocol was approved by the institutional review board and was reviewed annually.

Treatment Plan

Eligible participants were planned to receive GEM 750 mg/m² as intravenous piggyback (IVPB) over 30 minutes followed by CDDP 25 mg/m² over 1 hour given on Days 1, 8, and 15 of a 28-day cycles. The recommended premedication for CDDP was dexamethasone 10 mg and granisetron 1 mg or ondansetron 32 mg administered IV, and adequate pre-hydration.

Treatment cycles were administered in the outpatient setting every 4 weeks unless there was evidence of disease progression, delay in treatment >3 weeks, or unacceptable toxicity.

Evaluations During Treatment

Pretreatment evaluations included the following: history and physical examination; complete blood count with differential; biochemical profile; electrocardiogram; and chest x-ray, computed tomography (CT) scan, and documentation of tumor measurements. During treatment, complete blood cell counts were performed weekly. History and physical examinations and assess-

ment of toxicities were performed before each cycle of treatment. Computed tomography scans were repeated after 2 cycles to assess response. Patients with stable disease (SD), complete response (CR), or partial response (PR) continued in the study and underwent repeat CT scan every 2 cycles or earlier at the discretion of the treating physician. Treatment toxicities were graded by South Western Oncology Group (SWOG) criteria.

Monitoring of Toxicity and Dose Adjustments

Patients were examined and graded each treatment day for evidence of toxicity according to the SWOG criteria. Dose adjustments were required based upon nadir counts and interim non-hematologic toxicities as follows.

If patients experienced febrile neutropenia or had granulocyte count less than 1000/UI or platelet count of less than 100,000/ μ L, doses of both GEM and CDDP were reduced to 75% of the previous dose in all subsequent treatments. If the ANC was less than 500/ μ L or the platelet count was less than 50,000 / μ L, CDDP and GEM were given at 50% of the previous dose after hematologic recovery. The use of growth factors was allowed, but no dose escalation above the original dose level should be performed on patients taking granulocyte colony-stimulating factor. If the patient experienced Grade 3 or 4 nephrotoxicity, CDDP dose was reduced to 50% for creatinine clearance (CrCl) of 40-59 mL/min and CDDP was held for CrCl <40 mL/min. If patients experienced other Grade 3 or 4 nonhematologic toxicities (except alopecia), treatment was held for up to 2 weeks; treatment resumed if nonhematologic toxicity had resolved to Grade 2.

Response Criteria

Responses were assessed by physical

Table 3. Frequency of Grade 3 and 4 Toxicities Among 9 Patients With SCCHN Who Received a Total of 17 Cycles of GEM Plus CDDP.

Toxicity	Grade 3 (no. patients)	Grade 4 (no. patients)	Total
Neutropenia	2	1	3
Thrombocytopenia	1	2	3
Asthenia	1	0	1
Death			1

exam of palpable lesions, medical photography, or by CT scan. Complete response was defined as complete disappearance of all clinically evident malignant disease. No new lesions could appear during that time, and there could be no evidence of nonevaluable disease. Partial response applies only to patients with at least 1 measurable lesion and was defined as a $\geq 50\%$ decrease in the sum of the products of the perpendicular diameters of all measurable lesions. All measurable and evaluable lesions and sites were assessed.

Progressive disease was defined as a $\geq 25\%$ increase in the sum of the products of measurable lesions over the smallest sum observed or over baseline if no decrease, reappearance of any lesion that had disappeared, or appearance of any new lesion or site. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed. Stable disease was defined as any disease that did not qualify for CR, PR, or progression.

RESULTS

Patient Characteristics

Nine patients with recurrent or metastatic SCCHN were enrolled in the study between November 1997 and January 2000. All received at least 1 cycle of chemotherapy except for 1 patient who died after receiving 1 dose of chemotherapy. Patient characteristics are listed in Table 1. The median age of the patients was 59 years (range, 38-75 years). Seven of the participants were men. Four patients had their primary SCCHN in

the oral cavity, 3 in the larynx, and 1 each in the hypopharynx and parotid gland. All patients had received prior radiation therapy but none had received prior chemotherapy. The median number of cycles delivered was 2 (range, 0-4 cycles).

Treatment Responses and Survival

Nine patients received a total of 17 cycles of GEM plus CDDP chemotherapy while enrolled in this phase II study. Only 2 patients responded, for an overall response rate of 22%, with time to progression in the 2 responders 12 and 21 weeks (Table 2).

The 2 patients who achieved response included 1 patient who met criteria for partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) and 1 patient who had a minor response and met criteria for stable disease by RECIST. Both responders progressed at 21 and 21 weeks, respectively, as did 5 of 9 patients who progressed on therapy. Two patients were non-evaluable due to death before treatment evaluation. Among all 9 assessable patients, the median overall survival is 17.8 weeks.

Adverse Events During Treatment

The number of patients experiencing Grade 3 and 4 toxicities during treatment is listed in Table 3. Hematologic toxicity was common, including neutropenia Grade 3 (22% of patients) and Grade 4 (11%), and thrombocytopenia Grade 3 (11% of patients) and Grade 4 (22%). There were 2 episodes of neutropenic fever (22% of patients). Three

patients (33%) experienced Grade 3-4 thrombocytopenia, but there was no bleeding episodes. One patient died within 24 hours of receiving chemotherapy first cycle; his death was due to respiratory failure.

DISCUSSION

Chemotherapy in metastatic or locally advanced SCCHN produces only limited responses of short duration with a median survival of 4-6 months.¹ The combination of GEM plus CDDP has modest activity in patients with advanced recurrent or metastatic SCCHN, with an overall response rate of 22%. Only 2 responses were observed among the 9 patients studied; those responses were short (12 and 21 weeks) and at the expense of significant toxicity, with hematologic and non-hematologic toxicity and 1 death related to chemotherapy. These results reflect the lack of effective salvage therapy for patient who developed recurrent or metastatic disease following local treatment with surgery and radiation therapy.

The activity of GEM as a single-agent therapy was assessed in a phase II trial by SWOG in patients with recurrent or metastatic SCCHN. A total of 26 eligible patients were registered to receive a dose of 1,250 mg/m² weekly for 3 weeks, followed by 1-week rests. The treatment was well tolerated, but there were no objective treatment responses, with a median survival of 6 months.⁹

The combination of GEM and CDDP was studied in a slightly different dose schedule to the one we performed where CDDP was given at a dose of 50 mg/m² on Days 1 and 8 with GEM at a dose of 800 mg/m² at Days 1, 8, and 15 in a 4-week cycle. Of the 24 patients included, 11 cases had advanced recurrent locoregional disease while 13 patients had metastatic disease. An overall response rate of 22.7% was observed with the main toxicity being hematological.¹⁰

Gemcitabine plus CDDP chemotherapy is only modestly active in patients with recurrent or metastatic SCCHN; it offers a low response rate and significant toxicity. Further exploration of GEM combinations in different doses and schedules, especially with infusional GEM, may be worthwhile.

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