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Continuous infusion of 5-FU with split-dose cisplatin: An effective treatment for advanced squamous-cell carcinoma of the head and neck

Abstract

Purpose: The purpose of this study was to determine if a combination chemotherapy, using continuous intravenous infusion of fluorouracil (5-FU) in combination with split-dose cisplatin, in patients with recurrent or metastatic head and neck squamous-cell could improve previously reported clinical outcomes.

Methods: Forty-two patients with recurrent or metastatic head and neck squamous-cell cancer were treated by cisplatin (25 mg/m²/day on days 1-3) and 5-FU (750 mg/m²/day for 120 hours; continuous intravenous infusion on days 1 through 5) with a cycle that repeated every 3 weeks.

Results: Of the 42 patients, 8 (19.1%) showed complete response and 12 (28.5%) demonstrated a partial response, giving an overall response rate of 47.6%. Response rates were significantly different for patients undergoing initial treatment *vs.* re-treatment: 73.6% (14/19) *vs.* 25.9% (6/23), respectively ($\chi^2=9.45$, $P<0.05$). Median time to progression was 7.2 months and median overall survival was 13.7 months. The 1 year survival was 57.1%. Toxicity mainly included myelo-suppression, mucositis, nausea and vomiting.

Conclusion: Chemotherapy with 5-FU by continuous intravenous infusion in combination with split-dose cisplatin is effective with a tolerable toxicity profile in patients with recurrent, or metastatic squamous-cell carcinoma of head and neck. The overall response was significantly higher in patients undergoing initial treatment in comparison with patients undergoing re-treatment after relapse.

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Head and neck carcinoma (HNC) affects approximately 500,000 patients each year worldwide. Despite advances in treatment methods, the prognosis for patients diagnosed with HNC is poor and more than one-third of these patients relapse and advance to terminal stages. Recurrent and/or metastatic squamous cell carcinoma is considered the main indication for chemotherapy, especially when operative and radiotherapeutic options have been exhausted. Chemotherapy has been used extensively in these patients and many chemicals have been shown to be pharmacologically active. The choice of therapy for recurrent HNC depends on the location, size or extent of the tumor, the presence or absence of distant metastases, previous therapy and the Karnofsky Performance Status of the patient [1-5]. Platinum-based combination regime, typically cisplatin plus 5-fluorouracil (5-FU), is the most commonly used chemotherapy regime for patients diagnosed with HNC. Combination chemotherapy with cisplatin and 5-FU achieves about 30% recovery, as reported in a series of randomized clinical studies [7-9]. Reported response rates vary between 11% and 79%, with an average sample size of 30 patients.

The regimen of cisplatin and 5-FU are generally high-dose cisplatin (100 mg/m² for day 1) and continuous 5-FU (1000 mg/m² administered via 24-hour infusion for days 1-4), and repeated after 21 days. During treatment, patients must intake large amounts of fluid and side effects including severe nausea and vomiting are often reported.

We have developed a novel treatment regimen that incorporates continuous intravenous infusion 5-FU (days 1-5) and split-dose cisplatin (days 1 to 3) for patients with advanced squamous-cell carcinoma of the head and neck could lead to improved clinical outcomes. The aim of this study was to evaluate whether the efficacy and toxicity profile of our continuous intravenous infusion of 5-FU in combination with split-dose cisplatin.

Patients and Methods

Patients

All patients with histological confirmed recurrent or metastatic head and neck squamous cancer were eligible for inclusion in this study. Other inclusion criteria included: aged between 18 and 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, and presence of a measurable disease. Patients who had previously received chemotherapy were also eligible except in cases where prior chemotherapy regimens contained continuous intravenous infusion of 5-FU.

Patients were excluded if they had received chemotherapy within 4 weeks of enrollment, had an absolute neutrophil

count of <1,500/ml and platelet count of <100,000/ml, had abnormal hepatic and renal functions (defined as bilirubin, AST and ALT > 1.5 times the upper normal limit (UNL), alkaline phosphatase > 5xUNL, and a calculated or actual creatinine clearance <60 ml/min); reported or presenting with cardiac disease or other serious concomitant illnesses or medical conditions, had a previous malignancy other than cervical, basal or squamous cell cancer of the skin within 5 years of entry into the study, had psychological or sociological problems that precluded the patient's understanding of the study's implications and requirements. Patients with CNS metastasis, uncontrolled infection or life threatening medical conditions, and pregnant and lactating women were also excluded from the study. As a requirement of the study protocol, subjects must have been willing to receive continuous intravenous infusion. This study protocol was approved by the ethics and scientific committees and fully informed written consent was obtained from all patients prior to participation in any facet of the study.

Treatment plan

The regimen consisted of a 120 hour continuous intravenous infusion of 5-FU on days 1-5 and cisplatin on days 1 to 3. This protocol was repeated every 21 days. Treatment was discontinued if 1) there was evident disease progression, 2) unacceptable toxicity developed or 3) the patient completed 6 cycles chemotherapy. Cisplatin was infused, after appropriate hydration, at a dose of 25 mg/m² on days 1 to 3. 5-FU was infused continuously over 120 hours at a dose of 750 mg/m² beginning on day 1. Antiemetic medication consisted of 5-HT₃ receptor antagonists administered before the chemotherapeutic treatment. During the course of this treatment regimen, neither preventive G-CSF nor GM-CSF were used. A peripherally inserted central catheter (PICC) was used for intravenous access.

Patient evaluation

Baseline evaluations included complete medical history, physical examination, complete blood cell count with differential and platelet counts, complete blood chemistry and ECG. Computed tomography (CT) scans of the lesion were performed at study entry. Additional imaging studies were performed whenever clinically indicated. During treatment, complete blood cell counts were performed twice weekly. Blood chemistry and physical examination were performed as clinically indicated.

TABLE 1. Baseline patient characteristics

Total patients enrolled	42
Patients who completed the study	42
Male/female	29/13
Age (median)	28-67 (45)
Histology	
Poorly Differentiated squamous cell carcinoma	42
Therapy	
Initial treatment	19
Retreatment	23
ECOG performance status	
0	14
1	25
2	3
Distant disease sites	
Lung	31
Liver	18
Bone	11
Other sites	9
Previous treatment	
Radiotherapy	23
Chemotherapy	20

Clinical assessments and statistical analysis

Response rates were evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST) and the response rate was assessed within 4 weeks of the initial assessment [6]. CT scans were performed after every two cycles of treatment to evaluate tumor response. Overall survival (OS) was defined from the date of starting protocol treatment to death or last patient contact. Time to progression (TTP) was defined from the date of starting protocol treatment to the date of documented disease progression, death or last contact. One year survival was defined from the date of starting protocol treatment to survival for 1 year. Toxicity was graded according to the National Cancer Institute common toxicity criteria (NCI-CTC 2.0 version). The χ^2 test was used to compare the responses between patients who received therapy as their initial treatment and patients who received this as a re-treatment. The Kaplan–Meier method was used for the evaluation of survival curves and the log rank test was used for the comparison of the survival rates.

Results

Baseline characteristics of the patients

Forty-two patients (29 male, 13 female), with a median age of 45 years (range 28-67), were included in this study. Nineteen

TABLE 2. Efficacy of initial treatment and retreatment

	CR	PR	SD	PD	ALL
Total	8(19.1%)	12(28.5%)	12(28.5%)	10(23.8%)	42
Initial treatment	6(31.5%)	8(42.1%)	3(15.7%)	2(10.5%)	19
Retreatment	2(8.6%)	4(17.3%)	9(39.1%)	8(34.7%)	23

CR, complete remission; PR, partial remission; SD, Stable disease; PD, progressive disease

patients had no prior therapy (initial treatment) and 23 patients had relapsed after surgery, radiation therapy and/or chemotherapy (re-treatment). The primary tumor sites were as follows: hypopharynx: 8, oropharynx: 5, oral cavity: 2, larynx: 4, tongue: 2, maxillary sinus: 4, parotid gland: 5 and nasopharyngeal: 12. Thirty-five patients had distant metastasis in various regions including the lungs, liver, and bone. In the initial treatment group, all new diagnostic cases were stage IV and 12 of these patients had distant metastasis. All patients were evaluable for toxicity and response. Demographic characteristics and baseline scores are shown in Table 1.

Response and survival

Approximately 135 complete cycles of chemotherapy were given to the 42 patients. The mean cycle count was 3.2 cycles per patient (median: 4 cycles) with a range of 2 to 6. Among the 42 cases, the overall response rate was 47.6% (95% CI: 32.5%-62.7%). Complete remission (CR) occurred in 8 cases (19.1%), partial remission (PR) occurred in 12 cases (28.5%), stable disease (SD) was present in 12 cases (28.5%), progressive disease (PD) occurred in 10 cases (23.8%). Among the 19 initial treatment patients, overall response rate was 73.6% (95% CI: 53.8%-93.4%) and there were 31.5% (6/19) CR, 42.1% (8/19) PR, 15.7% (3/19) SD, 10.5% (2/19) PD among these patients. For the 23 retreatment patients, overall response rate was 25.9% (95% CI: 8.0%-43.8%) and there were 8.6% (2/23) CR, 17.3% (4/23) PR, 39.1% (9/23) SD, 34.7% (8/23) PD among these patients (Table 2). The overall response of initial treatment compared to that of re-treatment was significantly higher (73.6% vs. 25.9%, $\chi^2=9.45$, $P=0.002$).

With a median follow-up time of 20 months, overall median time to progression was 7.2 months. In the initial treatment group median time to progression was 10.6 months, which was significantly longer than the median of 6.5 months in the retreatment group ($\chi^2=4.288$, $P=0.038$). The overall median survival time was 13.7 months. The median survival time in the initial treatment group was 17.4 months, which was also significantly longer than the 9.7 months of the retreatment group ($\chi^2=6.550$, $P=0.010$). Kaplan–Meier curves of time to

FIGURE 1. Overall survival of all patients. (n=42 patients)

FIGURE 2. Overall survival of initial treatment (n=19 patients) vs. re-treatment patients (n=23 patients).

FIGURE 3. Time to progression of all patients (n=42 patients).

FIGURE 4. Time to progression of initial treatment (n=19 patients) vs. re-treatment patients (n=23 patients).

TABLE 3. Incidence of adverse events by toxicity grade

Adverse reaction	WHO Grade				
	0 (%)	I (%)	II (%)	III (%)	IV (%)
Nausea and vomiting	1(2.3)	20(47.6)	13(30.9)	8(19.0)	0(0.0)
Mucositis	18(42.8)	15(35.7)	7(16.6)	2(2.7)	0(0.0)
Leucopenia	4(9.5)	16(38.0)	20(47.6)	2(2.7)	0(0.0)
Neutropenia	6(14.2)	21(50.0)	15(35.7)	0(0.0)	0(0.0)
Anemia	24(57.1)	14(33.3)	4(9.5)	0(0.0)	0(0.0)
Thrombocytopenia	14(33.3)	23(54.7)	5(11.9)	0(0.0)	0(0.0)
Fever	35(83.3)	4(9.5)	3(7.1)	0(0.0)	0(0.0)
Liver dysfunction	32(76.1)	7(16.6)	3(7.1)	0(0.0)	0(0.0)

progression and overall survival are shown in Figs. 1-4. One year survival rate was 57.1%.

Toxicity

All patients were evaluated for toxicity. Grade 3 toxicity occurred in 28.5% (12/42) of the patients, and consisted mainly of hematological toxicity, leucopenia, nausea, vomiting and mucositis. Adverse reactions to treatment are summarized in Table 3.

During the treatment, leucopenia and neutropenia occurred in 90.5% (38/42) and 85.8% (36/42) of the patients, respectively. Grade 3 leucopenia occurred only in 2.7% (2/42) of the patients and no patients developed febrile neutropenia. Anemia and thrombocytopenia occurred in 42.8% (18/42) and in 66.6% (28/42) of the patients, respectively, but no patients required blood transfusions. Mucositis and nausea and vomiting were the most common non-hematological sign of toxicity and were present in 57.2% (24/42) and 97.7% (41/42) of the patients, respectively. Grade 3 mucositis occurred in 2.7% (2/42) of the patients. Nausea and vomiting were typically mild (Grade 1 and 2), and 19.0% (8/42) of patients demonstrated grade 3 nausea and vomiting. 54.7% (23/42) of patients were treated with ondansetron or granisetron and 38.0% (16/42) with metoclopramide. Non-infective drug related fever occurred in 16.6% (7/42) of patients.

Discussion

In the present study, a regimen of continuous intravenous infusion of 5-FU, in combination with split-dose cisplatin, was evaluated for the treatment of patients with advanced squamous-cell carcinoma of the head and neck to determine if clinical outcomes could be improved relative to current standard treatments. Cisplatin was infused at a dose of 25 mg/m² on days 1 to 3 and 750 mg/m² of 5-FU was given as a 120 hour continuous intravenous infusion beginning on day 1. The con-

tinuous infusion of 5-FU may be advantageous over traditional infusion regimens because the half-life of 5-FU is short; so continuous intravenous infusion 5-FU will likely induce more tumor cells enter to phase S – the phase which is responsive to chemotherapy.

The overall response rate was 42.7%, with a median TTP of 7.2 months, a median OS of 13.7 months and a 1 year survival rate of 57.1%. These results are similar to recent outcomes for patients on a traditional chemotherapy regimen [8-10]. Initial treatment patients had an overall response rate of 73.6% and a CR of 31.5%. These results are comparable to those of Kish [11-12], who reported that the combination of 96 hour 5-FU infusion + CACP produced a 90% overall response with 19% CR in 26 previously untreated patients with advanced disease. Kish *et al.* also reported a 70% overall response rate with 27% CR rate in 30 patients with recurrent disease. In contrast, the re-treatment patients in our study demonstrated an overall response rate of only 25.9% with 8.6% CR. Using the continuous intravenous infusion protocol described in our study, patients who were undergoing an initial treatment showed a clinically and statistically meaningful improvement in response to the treatment. It should be noted that the median survival in the study by Kish *et al.* was 27.5 weeks, which was shorter than the 13.7 months in our study [11].

Andreadis *et al.* [13] reported that, in the treatment of advanced oral cancer with 5-fluorouracil and cisplatin, the overall response to the induction chemotherapy was 52.3%, with 19% CR, and 33.3% PR and to the chemotherapy for recurrent/metastatic disease was 30.4% with 8.7% CR, 21.7% PR, and the median survival time of both initial treatment and re-treatment groups was 12 months. The survival time in the initial treatment group was 17.4 months compared with 9.7 months in the retreatment group. The median survival time of the patients in our study was slightly greater than the Andreadis study (13.7 months), which may be attributable to the greater number of initial treatment patients in our study group.

The side effects in our study were mild and mostly consisted of nausea and vomiting. Kish [10] reported leukopenia in 61% of patients and nausea and vomiting in 83% of the patients. Kish also reported incidents of stomatitis, which were more frequent on the infusion arm, but all incidents were mild and reversible. These findings coincide with the results from our study; leucopenia and neutropenia occurred in 90.5% and 85.8% of patients, respectively. Mucositis and nausea and vomiting were seen in 57.2% and 97.7% of patients, respectively, although the severity of these side effects were relatively mild, consisting of mostly grades 1 and 2.

The regimen evaluated in our study did not require excessive hydration and reduced the incidence and severity of nausea and vomiting relative to the traditional chemotherapy treatment regimens. The regimen utilized in our study is economically advantageous compared to Taxotere with PF or Cetuximab with PF for patients; however, Browman [14] reported that the addition of infusional fluorouracil to standard radiation in SCHNC improved the complete response rate and was associated with beneficial trends in progression-free and overall survival compared with radiation alone.

Recently, cetuximab monotherapy [15] as well as cetuximab in combination with platinum-based chemotherapy [16-17] have been used for patients with HNC, and have demonstrated encouraging initial results. Despite the potential benefits, future clinical studies with large sample sizes will be needed to establish possible superiority of cetuximab regimens.

In conclusion, these results indicate that continuous intravenous infusion 5-FU in combination with split-dose cisplatin is an active and well-tolerated regimen in patients with advanced squamous-cell carcinoma of the head and neck. This regimen is particularly advantageous for patients who are undergoing initial treatment.

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