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ORIGINAL ARTICLE

Retrospective analysis: concurrent chemoradiotherapy using protracted continuous infusion of low-dose cisplatin and 5-fluorouracil for T2N0 glottic cancer

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Abstract
Purpose. Treatment with conventional radiotherapy alone for local control of T2 glottic cancer (T2GC) is insufficient. To improve local control of T2GC, we have simultaneously administered continuous intravenous infusions of low-dose cisplatin and 5-fluorouracil (5-FU) in combination with irradiation.
Materials and methods. We performed this combination therapy in a total of 11 consecutive patients with previously untreated invasive squamous cell carcinoma (T2GC). Cisplatin was administered at 4 mg/m2/day and 5-FU at 200 mg/m2/day for 120 h, except during weekends, beginning on the day irradiation with a once-daily fraction at 2 Gy was started.
Results. An initial local control rate of the primary tumor was achieved in 10 of the 11 patients (91%), and ultimate laryngeal preservation by cordectomy was achieved in all cases. Regarding adverse reactions, grade 3 or 4 hemotoxicity did not develop in any of the patients. Grade 3 laryngitis was observed in four patients (36%), but none of these patients required interruption of treatment owing to acute laryngeal reactions.
Conclusion. Instead of radiotherapy alone, this combination chemoradiotherapy is suggested with the possibility of improving local control of T2GCs.

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Key words Early glottic cancer · Squamous cell carcinoma · Chemoradiation · Cisplatin · 5-Fluorouracil · Biochemical modulation

Introduction

Glottic carcinoma is the most common laryngeal cancer. Early glottic cancer is usually present as a localized disease and can be successfully treated with either radiotherapy or surgery. Radiotherapy has the advantage of preserving laryngeal structure and function in the majority of the patients. Therefore, radiotherapy is the treatment of choice for early-stage glottic carcinomas in most institutions, with surgery being reserved as a salvage option for local failures.

For T1 glottic lesions the local control rate for radiotherapy alone has been reported to be about 90%, whereas for T2 glottic cancer (T2GC) lesions the local control rate has been about 70%.[1–7] The rate of local control with radiotherapy for T2GC is low and thus insufficient. To improve local control by conventional radiotherapy, we have simultaneously administered continuous intravenous infusions of low-dose cisplatin and 5-fluorouracil (5-FU) in combination with irradiation to treat patients with esophageal or lung cancer.[8,9] This combination therapy has resulted in relatively mild adverse effects, and the objective responses were encouraging. Therefore, we conducted a pilot trial to investigate the tumor response rate, toxicity, and local control rate of this concurrent chemoradiotherapy for T2GCs.

Materials and methods

Between March 1995 and November 1998, we performed this combination therapy in a total of 11 consecutive patients with previously untreated invasive squamous cell carcinoma of the true vocal cord classified as T2N0M0, according to the International Union Against Cancer (UICC, 1987) TNM classification system, at Aichi Cancer Center Hospital. Informed consent was obtained from all patients.

Table 1 shows patient and tumor characteristics. All patients were male, and the median age was 63 years (range 53–72 years). Two patients who were enrolled in this trial had concurrent secondary and primary cancers. Both of those patients also had lung cancer. One patient was treated with the combination therapy simultaneously for lung cancer. The other patient underwent surgery for lung cancer after the end of the combination therapy because when he was diagnosed with lung cancer the glottic cancer was already under treatment. The operation for lung cancer could not immediately performed after the end of this combination therapy for GC, because of year-end through New Year holidays.

Table 1. Patient and tumor characteristics

Total no. of patients	11
Age (years), median and range	63 (53–72)
Sex	
Male	11
Female	0
Performance status (ECOG)	
0–1	11
≥2	0
Syrchronous primary cancers	2
Histology	Squamous cell carcinoma
Grade	
Well differentiated	5
Moderately differentiated	1
Unknown	5
Type of lesion	
Exophytic	4
Infiltrating	7
Disease extent	
Supraglottic	8
Subglottic	2
Anterior commissure involvement	4
Bilateral vocal cords	1
Impaired vocal mobility	2
Transglottic	1

ECOG, Eastern Cooperative Group

The patients with disease extension to the supraglottis, subglottis, anterior commissure, and bilateral vocal cords are detailed in Table 1, as are the patients with impaired vocal mobility. Eligibility criteria, included a performance status of 0 to 3 (according to Eastern Cooperative Oncology Group criteria), creatinine clearance of ≥40 ml/min, leukocyte count of ≥3500/mm^3, platelet count of ≥100,000/mm^3, hemoglobin level of ≥10 g/dl, and glutamic oxaloacetic transaminase/glutamic pyruvic transaminase levels less than or equal to twice the upper limit of the normal range.

Concerning chemotherapy, low doses of cisplatin and 5-FU were continuously administered via different routes through a catheter placed in the central vein.[8,9] Figure 1 shows the treatment scheme for this combination therapy. In Japan, two-drug combination chemotherapy[10] that combines injection of a low dose of 5-FU with daily frequent administration of cisplatin has been commonly carried out. With this chemotherapy alone, the daily dose of 5-FU ranged from 300 to 500 mg, and that of cisplatin ranged from 5 to 10 mg. We determined the doses of 5-FU and cisplatin for T2N0 glottic cancer as follows. The daily dose of 5-FU was given at 200 mg/m^2, and that of cisplatin was 4 mg/m^2. Cisplatin and 5-FU were administered for 24 h every day except Saturdays and Sundays beginning on the day irradiation was started.

All patients were treated with parallel-opposed fields using ^{60}Co and received a continuous course of radiotherapy with a once-daily fraction at 2 Gy; the total radiation dose was up to 66 Gy. Wedge filters of 15° or 30° were used to improve dose homogeneity. The dose was evaluated at the isocenter of the field. Field size ranged

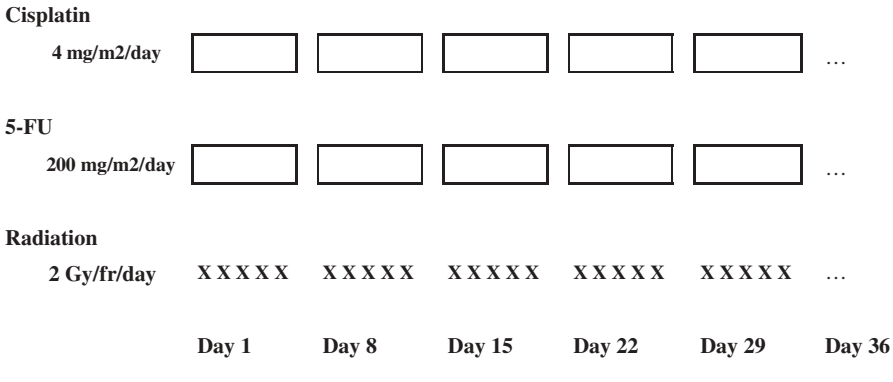

Fig. 1. Treatment scheme for concurrent chemoradiotherapy using protracted infusion of low-dose cisplatin and 5-fluouracil (5-FU)

from 25 to 36 cm^2. No prophylactic neck irradiation was performed in any of the cases. All patients were immobilized using a thermoplastic mask during treatment.

The stopping rule for chemotherapy and radiotherapy was the same as for esophageal cancer and lung cancer patients. When the leukocyte and platelet counts decreased to <2000/mm^3 and <50,000/mm^3, respectively, chemotherapy was discontinued. It was also discontinued when the serum creatine clearance became <30 ml/min. Radiotherapy was discontinued when leukocyte and platelet counts were <1500/mm^3 and <30,000/mm^3, respectively. When leukocyte and platelet counts were improved to 2000/mm^3 and <50,000/mm^3 or better, respectively, radiotherapy was resumed.

Adverse reactions were evaluated according to National Cancer Institute common toxicity criteria (Version 2.0, 1997). Primary effects were evaluated according to World Health Organization criteria. The endpoints in this study were local control and relapse-free survival. Kaplan-Meier methods were used for the analysis of local control, overall survival, and relapse-free survival curves.

All patients were treated on an inpatient basis.

Results

The median total radiation dose was 66 Gy (range 60–66 Gy). One patient who discontinued at 60 Gy refused further radiotherapy. The median overall treatment time was 47 days (range 43–52 days). In one patient, irradiation was interrupted for 3 days because of a catheter-related infection. Chemotherapy was continued for 5–6 weeks. In one case, however, chemotherapy was discontinued after 4 weeks owing to the patient's refusal to continue.

Of the 11 patients enrolled, complete response (CR) of the primary site was achieved in all cases. Two patients developed catheter-related infections. In one of these patients, radiotherapy and chemotherapy were interrupted; in the other patient, chemotherapy was discontinued.

The appearance of acute toxicity is shown in Table 2. Regarding adverse reactions, grade 3 or 4 hemotoxicity did not develop in any of the patients. As for laryngitis, grade 3 toxicity was observed in four patients (36%), but none of them required interruption of treatment due to acute laryngeal reactions. Grade 3 toxicity developed in two patients owing to infection from the catheter placed in the central vein.

The local control rate, relapse-free survival rate, and overall survival rate are shown in Fig. 2. The 5-year local control rate, 5-year relapse-free survival rate, and 5-year overall survival rate were 91%, 82%, and 73%, respectively.

Regarding the outcome of the patients after this therapy, 9 of the 11 patients are alive. The median follow-up for living patients was 54 months (range 42–78 months). Among the nine survivors, one patient developed a local recurrence after 3 months. This patient had undergone resection of the recurrent side of the vocal cord (cordectomy). Of the 11 enrolled, 1 patient died of myocardial infarction after 13 months, and another patient died of lung cancer after 26 months. However, there were no recurrences in the vocal cord in either case. Initial local control of the primary tumor was achieved in 10 of the 11 patients (91%), and ultimate laryngeal preservation was achieved in all cases. This combination therapy did not result in severe treatment-related late toxicity.

Table 2. Acute toxicity

	Grade[a]				
Parameter	0	1	2	3	4
Hematologic					
WBC count	4	4	3	0	0
Hemoglobin	8	2	1	0	0
Platelets	5	4	2	0	0
Laryngitis	0	0	7	4	0
Infection (catheter-related)	9	0	0	2	0

[a] National Cancer Institutes common toxicity criteria (version 2.0, 1997)

Discussion

In most institutions, the current standard of care for patients with T2GC is conventional radiation therapy

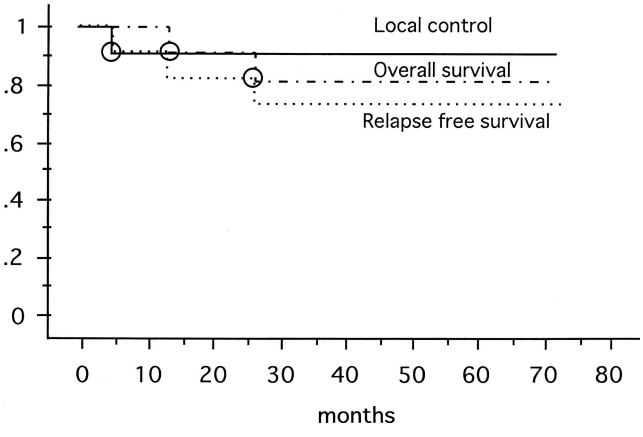

Fig. 2. Local control rate, relapse-free survival rate, and overall survival rate calculated using the Kaplan-Meier method

alone. For patients with tumors extending beyond the glottis or tumors with impaired vocal cord mobility, local failure remains an important issue. In several studies, to improve local control, hyperfractionation or increasing fraction size in once-daily fractionation[11–13] was performed. To improve local control by conventional radiotherapy, we have simultaneously administered continuous intravenous infusions of low-dose cisplatin and 5-FU in combination with irradiation to treat patients with esophageal or lung cancer.[8,9] In Japan, this two-drug combination chemotherapy has been commonly carried out.[10,14,15] Its administration is theoretically based on the biochemical mechanisms of the two agents. Our combination chemotherapy with the addition of radiotherapy resulted in relatively mild adverse effects, and the objective responses were encouraging.

With regard to hemotoxicity, in esophageal cancer patients the rates of grade 3 and 4 toxicity, reflected in the 0 white blood cell (WBC) and platelet counts, were 38% and 24%, respectively, whereas in lung cancer patients they were 8% and 0%, respectively.[8, 9] The hemotoxicity in this trial was not seen to be more severe than in patients with esophageal or lung cancer because of the much smaller irradiation field.[16] Compared with esophageal cancer and lung cancer patients, hemotoxicity in those with T2N0GC was slight. In those with acute toxicity, grade 3 laryngitis was an important issue. According to one report,[17] with irradiation alone the risk of grade 3 mucositis occurs in approximately 20%–30%, whereas with concurrent chemoradiotherapy with high-dose cisplatin/5-FU grade 3 mucositis occurs in approximately 60%–80%. When compared to other reports,[17] the amount of grade 3 laryngitis in this study was not high and was manageable. Hence, this combination therapy appears to be acceptable.

In addition, the local control rate of T2N0GC was good, suggesting that this combination therapy is a promising treatment method. With both esophageal cancer and lung cancer, it has been demonstrated that this combination therapy can be performed in elderly and high-risk patients owing to the high caloric transfusion through a catheter placed in the central vein. However, compared to patients with lung cancer or esophageal cancer treated by this combination therapy, in glottic cancer patients with a good performance status there may be a tendency to increased infection risk during the weekend hiatus. They go home on the weekend after locking the end of the catheter. In both esophageal cancer and lung cancer patients, catheter-related infection was not seen. We are afraid that the entry site of the catheter might have been vulnerable to infection for the above reason. We therefore think it is necessary to change the administration route from the central vein to a peripheral vein and to administer the chemotherapy only on an inpatient basis (i.e., require hospitalization for continuous infusion for 24 h.

From now on, for patients with T2N0GC we have decided to administer the chemotherapy via a peripheral venous route. At the same time, we have made a new start by hoping to offer these patients a chemoradiation protocol using the oral-uptake anticancer agent S-1, which can be taken on an outpatient basis. However, the optimal dose and maximum tolerated dosage of S-1 in combined chemoradiotherapy are unclear. Therefore, we are beginning with a Phase 1 study of single-agent chemoradiation using S-1. S-1 is a novel oral antimalignancy drug based on biochemical modulation of 5-FU and containing tegafur, gimestat (CDHP), and otastat potassium in a molar ratio of 1 : 0.4 : 1.[18]

Conclusion

The combination therapy we used was effective with only mild toxicity. Therefore, instead of conventional radiotherapy alone, we suggest it as a chemoradiotherapy regimen with the possibility of improving local control of T2GC.

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