Concomitant Chemoradiotherapy as a Standard Treatment for Squamous Cell Carcinoma of the Temporal Bone

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ABSTRACT

We sought to characterize the effectiveness of concomitant chemoradiotherapy (CCRT) for patients with squamous cell carcinoma of the temporal bone. We performed a retrospective chart review of 14 patients with cancer of the temporal bone who were provided initial treatment in our hospital from December 2001 to November 2008. Four patients with stage I tumors were treated by radiation therapy alone or with oral administration of S1. One patient with a stage II tumor was treated by radiation therapy concomitant with low dose docetaxel. Nine patients with stage IV tumors were treated by CCRT using the TPF regimen (docetaxel, cisplatin, and 5-fluorouracil). As an initial treatment, all patients but one were treated by radiation therapy with or without chemotherapy. Grade 4 adverse events of patients who received CCRT using the TPF regimen involved the leukopenia in one patient and the neutropenia in two patients. Local recurrences were observed in three patients including two patients with T4 tumors. Five-year disease-specific survival rates for all patients and for patients with T4 tumors were 78% and 67%, respectively. CCRT using the TPF regimen is safe and effective as the first treatment for patients with cancer of the temporal bone.

KEYWORDS: Squamous cell carcinoma of the temporal bone, chemoradiotherapy, TPF, survival rates

Although surgical treatment is effective for early stage cancers of the temporal bone, once cancers have invaded the skull base and/or the surrounding extra-temporal bone tissues, they are difficult to manage surgically and the prognosis of the patient becomes very poor. We reviewed the charts of patients with cancer of the temporal bone seen in our hospital before 2000 and realized that the prognoses of patients with T4 tumors were very poor. In particular, the prognoses of patients with nonresectable T4 tumors were extremely

poor, and their mean survival time was only several months. Because they had received chemoradiotherapy with various protocols and various antitumor agents, mainly platinum- and pyrimidine-based, we felt that the power of the chemotherapy protocol was not effective for curing the disease. As new chemotherapy protocols, including taxanes, have been developed, we decided in 2001 that concomitant chemoradiotherapy (CCRT) would be an effective treatment for squamous cell carcinomas of the ear. Although this is a pilot study

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to treat squamous cell carcinomas of the temporal bone, we herein report the encouraging results of our CCRT treatment.

PATIENTS AND METHODS

The study design was a retrospective chart review. Fourteen patients with cancer of the temporal bone, who had been provided initial treatment in our hospital from December 2001 to November 2008, were reviewed. All tumors were diagnosed as squamous cell carcinomas by histopathologic examination and were thought to have originated from the external auditory canal. Preoperative radiographic studies were performed on all patients and including computed tomography (CT), magnetic resonance imaging (MRI), and 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET). Patients were diagnosed and classified according to the University of Pittsburgh system,¹ and none of the patients had a distant metastasis at the time of diagnosis. The T classification was as follows: T1, tumor limited to the external canal without bony erosion; T2, tumor limited to the external canal with bony erosion; T3, tumor eroding the middle ear and/or mastoid, or causing facial paralysis with limited soft tissue involvement; T4, tumor eroding the cochlear, petrous apex, dura, or with extensive soft tissue involvement.

Four patients with stage I tumors were treated by radiation therapy alone or with oral administration of S1.² One patient with a stage II tumor was treated by radiation therapy concomitant with weekly administration of low-dose docetaxel.³ Nine patients with stage IV tumors were treated by CCRT using the TPF regimen,^{4,5} which consists of continuous intravenous administration of 600 to 700 mg/m² 5-fluorouracil from day 1 through day 5, and a bolus injection of 50 mg/m²

docetaxel and 60 mg/m² cisplatin on day 2. Radiation therapies were performed using 4 MeV Lineac and an equally divided protocol. Patients received 2 Gy/fraction radiation therapy every weekday (five fractions per week) and total doses were 70 Gy.

Adverse effects were noted and classified using National Cancer Institute's common toxicity criteria. When neutrocytopenia was observed in patients after chemotherapy, granulocyte-colony stimulating factor (G-CSF) was administered immediately according to the guidelines.

The Kaplan-Meier method was used to calculate the survival curves of the patients, and a log-rank test was used to examine significant differences.

RESULTS

The profiles of all patients are summarized in Table 1. There were six male patients and eight female patients, and their average age was 62 years old, ranging from 51 to 74 years old at the time of diagnosis. Nine patients had their tumor on the right side and five were on the left. Otorrhea was the most common symptom that these patients complained about, and 11 of the 14 patients had that symptom. One of the patients had facial nerve palsy at the time of diagnosis, which indicated parotid invasion of the tumor.

As an initial treatment, all patients but one were treated by radiation therapy with or without chemotherapy. Because one patient with a T1N0M0 tumor had undergone ipsilateral parotidectomy and postoperative radiation therapy several years before, she was referred to our hospital and underwent resection of the tumor. Nine of the patients had T4 tumors invading extratemporal bone tissues, and they received CCRT using the TPF regimen. Two courses of TPF chemotherapy were

Table 1 Clinical Features of the Patients

	Age	Gender	Side	Chief Complaints	TNM	Extratemporal Invasion
1	51	M	R	HI, otorrhea, otalgia	T4N1M0	Dura, JF
2	53	F	R	Otorrhea, FNP	T4N0M0	JF, VII, IX, X paralysis
3	56	F	R	Otorrhea	T4N2bM0	Parotid gland
4	59	F	L	Otorrhea	T4N0M0	ICA, MSB, skin
5	54	F	R	Otorrhea	T4N1M0	MSB, MJ
6	68	M	L	Tumor	T4N0M0	MJ, parotid gland
7	71	M	L	HI, otorrhea, otalgia	T4N0M0	PA, MJ
8	67	F	R	Otorrhea, otalgia	T4N2bM0	MSB, MJ, skin
9	58	M	L	Tumor	T4N2bM0	MJ, parotid gland, skin
10	58	F	R	Otorrhea	T2N0M0	
11	72	M	L	Otorrhea	T1N0M0	
12	71	M	R	HA, otorrhea	T1N0M0	
13	68	F	R	Tumor	T1N0M0	
14	74	F	R	Otorrhea	T1N0M0	

FNP, facial nerve palsy; HA, hearing aid; HI, hearing impairment; ICA, internal carotid artery; JF, jugular foramen; MJ, mandibular joint; MSB, middle skull base; PA, petrous apex.

Table 2 Treatment and Results

	Chemotherapy	RT (Gy)	Response	Follow-Up, Months	Outcome	Notes
1	TPF × 3*	40 + 30	CR	84	NED	3M, mastoidectomy, pathological CR
2	TPF × 2	60	CR	18	DOD	
3	TPF × 2	40 + 22	CR	46	NED	RT cessation by dermatitis, S-1 orally after CCRT
4	TPF × 2	40 + 30	CR	13	DND	
5	TPF × 2	40 + 26	CR	37	NED	S-1 orally after CCRT
6	TPF × 1	40 + 30	PR	17	DOD	Refused 2nd course of TPF
7	TPF × 1	70	CR	26	NED	Cessation of 2nd course TPF by liver dysfunction
8	TPF × 2	50 + 20	CR	4	NED	
9	TPF × 2	40 + 30	CR	4	NED	
10	DOC × 6	50 + 20	CR	31	NED	
11	S-1	70	PR	38	NED	5M, salvage surgery
12	S-1	70	CR	38	NED	PH: DM
13	—	60	CR	4	NED	
14	—	—		17	NED	PH: irradiation after parotidectomy

*One course of induction chemotherapy and two courses of TPF were conducted.

CR, complete response; DM, diabetes mellitus; DND, dead not of disease; DOD, dead of disease; M, months; NED, no evidence of disease; PR, partial response; PH, past history; RT, radiotherapy; TPF, docetaxel, cisplatin, and 5-fluorouracil regimen.

performed for all but two patients who underwent CCRT using the TPF regimen. Two patients received one course of TPF chemotherapy, one of whom refused the second course of TPF and the course of the other was canceled because of liver dysfunction. Patients with squamous cell carcinomas of the ear were irradiated with 60 to 70 Gy radiation and the average dose was 67.5 Gy.

Adverse events of patients who received CCRT with the TPF regimen are summarized in Table 2. A grade 4 adverse event involving the leukocyte count was observed in one patient, and adverse events involving the granulocyte count were observed in two patients. Grade 3 adverse events involving bone marrow suppression were also observed in three patients involving the leukocyte count, in one patient involving the neutrophil count, in six patients involving the lymphocyte count, and in one patient involving the hemoglobin level. Grade 3 adverse events were observed in one patient of glutamic oxaloacetic transaminase (GOT) and in two patients with hyponatremia. One of the patients (case 7) showed liver dysfunction (GOT, grade 3) and the second course of TPF was canceled. Radiotherapy was canceled in one patient (case 3) because of radiation dermatitis.

A complete response (CR) was obtained for 11 of the primary tumors of patients who received CCRT and a partial response was obtained for two primary tumors. A CR was obtained in five patients who had cervical lymph node metastases and received CCRT. The CR rates were 78% and 100% for primary tumor and for cervical lymph node metastasis, respectively. Fig. 1 shows contrast-enhanced CT images for one patient (case 4) before and in the middle of the therapy. It is obvious that CCRT using the TPF regimen was very effective in shrinking the tumor. Fig. 2 shows the histopathology of the tumor specimen of another patient

(case 1). This patient received one course of induction chemotherapy using the TPF regimen plus CCRT, and a mastoidectomy was performed 3 months after the initial treatment. Tumor cells had disappeared in the posttherapeutic specimen, and we defined this as a CR pathologically.

Local recurrences were observed in three patients, including two patients with T4 tumors. One of those T4 patients refused the second course of chemotherapy, and salvage surgery was performed and was effective in one patient with a T1N0 tumor. Two patients with T4 tumors died of recurrent disease. One patient (case 4) died of an acute abdomen 13 months after the initial treatment. When disease-specific survival rates were calculated using the Kaplan-Meier method (Fig. 3), the 5-year disease-specific survival rate of all patients and of patients with T4 tumors were 78% and 67%, respectively (Table 3).

DISCUSSION

We emphasize that this is the first study to report that CCRT should be a standard treatment for squamous cell carcinoma of the temporal bone.

Cancer of the temporal bone is a relatively rare tumor among head and neck malignancies, and effective treatment strategies have not been established so far. Because of the anatomic complexity, surgical resection is relatively hard to carry out, especially for advanced cases that have invaded the temporal bone and the surrounding extratemporal bone tissues. As the surgical margins of these tumors are hard to estimate during surgery and are not obvious in some cases, pathological examination occasionally reveals that the surgical margin is tumor-positive. Moreover, because

Figure 1 Computed tomography findings of case 4. (A) Before treatment; the tumor had invaded into the parapharyngeal space and the parotid gland. (B) In the middle of concomitant chemoradiotherapy; one course of TPF (docetaxel, cisplatin, and 5-fluorouracil regimen) and 40 Gy of radiation therapy had been completed and the tumor had almost disappeared.

radical surgery involves resection of the temporal bone to some extent, it often results in an unfavorable quality of life (e.g., facial nerve palsy, hearing impairment, and so on).

A new protocol of chemotherapy using docetaxel, cisplatin, and 5-fluorouracil (the TPF regimen) has been adapted to treat squamous cell carcinomas of the head and neck, and its efficacy has been elucidated.^{4,5} Several reports have revealed that induction chemotherapy using the TPF regimen is significantly effective in patients with head and neck cancers.^{6,7} We performed a phase I trial of CCRT using the TPF regimen for patients with squamous cell carcinomas of the head and neck, and the recommended dose of docetaxel and cisplatin was estimated (Shiga K et al, in preparation).

We reviewed the charts of patients with cancers of the temporal bone seen in our hospital before 2000 and realized that the prognoses of patients with T4 tumors were very poor. In particular, the prognoses of patients

with nonresectable T4 tumors were extremely poor, and their mean survival time was only several months. Although those patients had received chemoradiotherapy with various protocols and various antitumor agents, the power of the chemotherapy protocol used was not effective in curing their disease. Therefore, we devised a strategy for treating patients with squamous cell carcinomas of the temporal bone, especially T4 tumors, using CCRT.

The main adverse event of CCRT using the TPF regimen was bone marrow suppression. A grade 4 adverse event involving the leukocyte count was experienced in one patient, and those involving the neutrophil count in two patients. Grade 3 adverse events concerning bone marrow suppression were also observed in three patients involving the leukocyte count, in one patient involving the neutrophil count, in six patients involving the lymphocyte count and in one patient involving the hemoglobin level. Other grade 3 adverse events were

Figure 2 Histopathology of the tumor tissue of case 1. (Left) Hematoxylin-eosin staining of the biopsy specimen before treatment. Squamous cell carcinoma cells with keratinization had invaded the interstitial tissues. (Right) Hematoxylin-eosin staining of the surgical specimen after treatment. Carcinoma cells had completely disappeared and hyalinization is observed. It was diagnosed pathologically as a complete response.

GOT (ALT) and hyponatremia observed in one patient and two patients, respectively. Neutropenia was effectively treated with G-CSF and there was no cause to halt the therapy. We conclude that CCRT using the TPF regimen is a safe and effective treatment for patients with cancers of the temporal bone.

Although this is a retrospective study that includes a limited number of patients, it suggests that CCRT would be effective for treating patients with cancers of the temporal bone, especially advanced cases whose tumors have invaded the temporal bone and

surrounding tissues. As can be seen in Fig. 1, the tumor invading the parapharyngeal space and the parotid gland had almost disappeared after one course of chemotherapy and 40 Gy of radiation therapy. This patient had a CR after all courses of CCRT were completed. Although thorough examination of the tissue specimens

Figure 3 Survival curves of the patients. Disease-specific survival rates were calculated by the Kaplan-Meier method. The 5-year survival rate of all patients was 78% (open squares), and of T4 and stage IV patients was 67% (open circles).

Table 3 Adverse Events of Patients Who Received Chemoradiotherapy Using TPF

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes		1	3	1
Granulocytes	2	2	1	2
Lymphocytopenia	1	2	6	
Hemoglobin	5	3	1	
Platelets	2			
Bilirubin	1			
ALP	2	1		
γ -GTP	1	1		
GOT (AST)	3	1	1	
GPT (ALT)	2	2		
Albumin	5	2		
Creatinine	2			
Hyponatremia	4		2	
Hyperkalemia	3	1		
Hypokalemia	1	■	■	■

ALP, alkaline phosphatase; ALT, alanin transaminase; AST, aspartate transaminase; GOT, glutamic oxaloacetic transaminase; γ -GTP, γ -glutamyl transpeptidase; GPT, glutamic pyruvic transaminase; TPF, docetaxel, cisplatin, and 5-fluorouracil regimen.

after treatment was explored in only one case, the effect of CCRT can be seen in the surgically removed sample of case 1 (Fig. 2). This patient showed a pathological CR, and the prognosis of this patient was very good.

Treatment options for tumors involving the ear or temporal bone have been few so far. Surgical resection followed by radiation therapy has been thought to be the best option. Lewis and Page⁸ reported a poor success rate with a variety of mastoidectomy procedures including modified radical and radical mastoidectomy or piecemeal resection for advanced cancer. Prasad and Janecka⁹ concluded that only external auditory canal carcinomas that are restricted to the canal but that involve the bone have equally good results from mastoidectomy or from lateral or subtotal temporal bone resection. When the disease has extended into the middle ear, patients who had subtotal temporal bone resection had a better survival ratio than patients who had lateral temporal resection or a mastoidectomy, although the difference was not statistically significant. Currently, if the tumor involves the middle ear, en bloc subtotal temporal bone resection is recommended as the surgical procedure of choice.

Local recurrences were observed in only three patients, including two patients with T4 tumors, and salvage surgery was performed effectively in one patient with a T1N0 tumor. The 5-year disease-specific survival rates of all patients and of patients with T4 tumors were 78% and 67%, respectively, although the observation time is relatively short in some cases. These results are better than any other treatment for cancer of the temporal bone that has been reported so far. For example, according to several reports describing the outcome of surgery, the 5-year survival rates of patients with T4 or stage IV tumors who underwent surgery were reported to range from 12.5 to 38%, although those studies included preoperative and postoperative radiation therapy.^{10–16}

Because this study is a pilot study of a small group of patients with cancers of the temporal bone, a randomized control study is needed to gather more information and to validate the efficacy of CCRT to treat cancers of the temporal bone.

CONCLUSION

CCRT using the TPF regimen is safe and effective as the first treatment for patients with advanced cancers of the temporal bone. Our treatment strategy seems to be the best approach and should be a standard method for treating patients with squamous cell carcinomas of the temporal bone.

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