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THE CLINICAL AND HISTOPATHOLOGICAL EFFECTS OF COMBINED CHEMOTHERAPY USING CISPLATIN AND PEPLOMYCIN TO TREAT CANCER OF THE TONGUE

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ABSTRACT

Combined chemotherapy (PP therapy) using cisplatin (CDDP) and peplomycin (PEP) was performed as induction chemotherapy for 31 patients with cancer of the tongue, and the clinical and histopathological effects were investigated. As the primary clinical effect, complete response (CR) was observed in three cases, partial response (PR) in 20 cases, minor response (MR) in six cases and no change (NC) in two cases, with a clinical response rate of 74.2%. The histopathological effects of the chemotherapy in the following cases showed these histological Grades: 0 or I in four cases, IIa in 12 cases, IIb in eight cases, III in six cases and IV in one case. Fifteen of the 31 patients who received PP therapy showed a histological Grade of IIb or better, representing 48.4% of the histopathological response rate. With regard to the mode of invasion of the tumor, the histopathological response rate was 90.0% in patients with invasive Grades 1 and 2, 41.7% in those with invasive Grade 3 and 16.7% in those with invasive Grade 4C. There were no patients with invasive Grade 4D in whom the therapy was histopathologically effective. In other words, the histopathological effect significantly decreased as the invasive Grade increased. With regard to the relationship between clinical effects and histopathological effects, there was one CR patient who showed a histological Grade of IIa. Thus, it is noteworthy that clinical effects were not necessarily consistent with post-chemotherapeutic histopathological effects.

Key Words: Cancer of the tongue, Chemotherapy, Cisplatin, Peplomycin, Histopathological effects

INTRODUCTION

CDDP, a platinum compound discovered by Rosenberg et al.[1] in 1965, has been used widely in the treatment of oral cancer since its antitumor effect was demonstrated on various carcinomas.[2–5] In recent years, the high efficacy of multiple-drugs combined therapy has also been noted,[6–8] and chemotherapy mainly using CDDP has attracted attention. PP therapy in particular, which is a combination of CDDP and PEP, is thought to have a synergistic effect and is currently included among the intensive treatments used for induction chemotherapy in oral cancer.[9–11] The primary clinical effects and histopathological effects of PP therapy given as preoperative chemotherapy for cancer of the tongue were investigated in the present study. Since some previous reports have shown that the therapeutic effect and prognosis of oral cancer are related to the tumor's mode of invasion,[12–13] the relationship between this mode of invasion and its histopathological effects was also investigated.

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SUBJECTS AND METHODS

In this study, 31 patients (22 males and nine females; ranging in age from 27 to 69 years, with a mean age of 48.7 years) with primary cancer of the tongue were treated at the Department of Oral Surgery of Nagoya University Hospital. In clinical staging, six patients showed Stage I, 13 Stage II, nine Stage III and three Stage IV (clinical staging: Stage I: T1N0M0, Stage II: T2N0M0, Stage III: T3N0M0 or T1, 2, 3N1M0 and Stage IV: T4N0, 1M0 or T1 ~ 3N2, 3M0).[14] The histopathological diagnosis was squamous cell carcinoma in all 31 patients. Histological grading of the mode of invasion (invasive Grade) showed 10 patients with invasive Grade 1 or 2, 12 with invasive Grade 3, six with invasive Grade 4C and three with invasive Grade 4D. Histological grading of invasive Grade was outlined by Yamamoto et al.[12] as follows: invasive Grade 1: a well-defined borderline; invasive Grade 2: cords present with a less marked borderline; invasive Grade 3: groups of cells with no distinct borderline; invasive Grade 4C: a diffuse invasion of cord-like structures and invasive Grade 4D: a diffuse invasion of diffuse type.[12] PP therapy was performed as preoperative chemotherapy, followed by tumor resection.

The treatment regimen included intravenous PP and PP intra-arterial infusion therapy sequentially administered. PP intravenous infusion therapy consisted of a dose of CDDP (80—100 mg/d) administrated over 1 h on day 1, followed by a 1 h infusion of PEP (5—10 mg/d) from days 2 to 6. PP intra-arterial infusion therapy consisted of a CDDP dose (20 mg/d) administrated around the clock for 5 consecutive days, followed by a 24 h infusion of PEP (5—10 mg/d) from days 6 to 10. All patients received two courses as a rule. The mean dose was 174.6 mg of CDDP and 74.3 mg of PEP.

In evaluating the clinical effects, the therapy was considered effective in patients who showed PR or better according to the criteria for therapeutic effects established by the Japan Society for Cancer Therapy.[15] The histopathological effects of chemotherapy were evaluated from specimens collected while in surgical resection. The therapy was considered effective in patients who showed a histological Grade of IIb or better according to the classification proposed by Shimosato and Oboshi.[16] The grading of histopathological effects by Shimosato and Oboshi (histological Grade) is as follows: histological Grade 0: no response; histological Grade I: characteristic changes are noted in tumor cells but tumor structures are not destroyed; histological Grade IIa: mild destruction of tumor structures i.e., "viable tumor cells" are frequently observed; histological Grade IIb: severe destruction of tumor structures, that is, "viable tumor cells" are few in number; histological Grade III: markedly altered, presumably non-viable tumor cells are present alone or in small clusters and "viable cells" are hardly seen; histological Grade IV: no tumor cells are present in any section. Significant differences were analyzed using the χ^2 test.

RESULTS

1. The relationship between clinical effects and the clinical stage

In Table 1, the primary clinical effect was CR in three cases, PR in 20 cases, MR in six cases and NC in two cases. The overall clinical response rate was 74.2% when a response of PR or better was regarded as effective. According to the clinical stage, the clinical response rate was 83.3% for clinical stage I, 76.9% for clinical stage II, 77.8% for clinical stage III and 33.3% for clinical stage IV. The clinical response rate for clinical stages I and II early cancers was 78.9%. Although there was no significant difference, the rate was higher than 66.7% in clinical stages III and IV progressive cancers (Table 1).

Table 1. The relationship between clinical effects and the clinical stage (number of patients and clinical response rate).
Clinical response rate: (number of patients with a clinical effect of PR+CR/number of patients with a clinical effect of NC+MR+PR+CR) × 100.

Clinical Effect / Clinical Stage	NC	MR	PR	CR	Clinical Response Rate (%)
I		1	3	2	83.3] 78.9
II	1	2	9	1	76.9
III		2	7		77.8] 66.7
IV	1	1	1		33.3
Total	2	6	20	3	74.2

2. The relationship between histopathological effects and the clinical stage

Post-chemotherapeutic histopathological effects were investigated using the Shimosato and Oboshi classification system. In Table 2, four patients showed histological Grade 0 or I, 12 showed histological Grade IIa, eight showed histological Grade IIb, six showed histological Grade III and one showed histological Grade IV. Assuming that the PP therapy was regarded as effective in patients whose post-chemotherapeutic histological findings were Grade IIb or better, the therapy was effective in 15 patients, with a histopathological response rate of 48.4%. In a similar manner, post-chemotherapeutic, histopathological effects were investigated according to the clinical stage classification. The histopathological response rate was 57.9% in clinical stages I and II patients. Although there was no significant difference, the rate was higher than 33.3% in clinical stages III and IV patients.

Table 2. The relationship between histopathological effects and the clinical stage (number of patients and histopathological response rate).
Histopathological response rate: (number of patients with histological Grade IIb+III+IV/number with patients of histological Grade 0, I+IIa+IIb+III+IV) × 100.

Histological Grade / Clinical Stage	0, I	IIa	IIb	III	IV	Histopathological Response Rate (%)
I		2	2	2		66.7] 57.9
II	2	4	3	3	1	53.8
III	1	5	2	1		33.3] 33.3
IV	1	1	1			33.3
Total	4	12	8	6	1	48.4

3. The relationship between histopathological effects and the invasive Grade

Post-chemotherapeutic histopathological effects were investigated according to the invasive Grade. In Table 3, a histological Grade IIb effect (or better) was observed in nine (90%) of 10 patients with invasive Grade 1 or 2, five (41.7%) of 12 patients with invasive Grade 3, one (16.7%) of six patients with invasive Grade 4C and none of the three patients with invasive Grade 4D. The histopathological response rate in patients with invasive Grades 4C and 4D was only 11.1%, significantly lower than 63.6% in patients with invasive Grades 1, 2 or 3 ($p < 0.01$).

Table 3. The relationship between histopathological effects and the invasive Grade (number of patients and histopathological response rate).
Histopathological response rate: (number of patients with histological Grade IIb+III+IV/number of patients with histological Grade 0, I+IIa+IIb+III+IV) × 100.

Histological Grade / Invasive Grade	0, I	IIa	IIb	III	IV	Histopathological Response Rate (%)	
1, 2		1	5	3	1	90.0	] 63.6
3		7	3	2		41.7	**
4C	2	3		1		16.7	] 11.1
4D	2	1				0.0	
Total	4	12	8	6	1	48.4	

(**: $p < 0.01$)

4. Th relationship between post-chemotherapeutic histopathological effects and clinical effects

Post-chemotherapeutic histopathological effects were investigated based on clinical effects. In

Table 4. The relationship between post-chemotherapentic histopathological effects and clinical effects (number of patients and histopathological response rate).
Histopathological response rate: (number of patients with histological Grade IIb+III+IV/number of patients with histological Grade 0, I+IIa+IIb+III+IV) × 100.

Histological Grade / Invasive Grade	0, I	IIa	IIb	III	IV	Histopathological Response Rate (%)	
NC	1	1				0.0	] 0.0
MR	2	4				0.0	**
PR	1	6	8	5		65.0	] 65.2
CR		1		1	1	66.7	
Total	4	12	8	6	1	48.4	

(**: $p < 0.01$)

Table 4, among the eight patients who showed NC or MR, three showed histological Grade 0 or I and five showed Grade IIa, indicating that the histopathological effects were poor. Among 20 patients who showed PR, however, there was one histological Grade 0 or I, six histological Grade IIa, eight histological Grade IIb and five histological Grade III, indicating a considerably wide distribution. It is noteworthy that in one of three patients in whom CR was achieved clinically, the histological effect was Grade IIa.

DISCUSSION

The use of CDDP in the treatment of head and neck cancers was first reported by Lippman et al.[17] Since Wittes et al.[18] confirmed its usefulness, many studies have been performed. Thereafter, the usefulness of this drug has been recognized in combination with bleomycin (BLM) and methotrexate (MTX). Since combined chemotherapy using CDDP and PEP was experimentally reported by Masuno[19] and Ekimoto et al.[20] to have a synergistic effect, the efficacy of this combination has been clinically reported as well.[9–11] The clinical response rate was 74.2% in the present study, which was approximately the same as or slightly higher than those in previous studies.

Many studies on the histopathological effects of chemotherapy for oral cancer have confirmed the effects of BLM and PEP. According to reports on the single administration of BLM, 13 (39.4%) of 33 patients with oral cancer in the report by Ozeki[21] and 21 (29.2%) of 72 patients in the report of Amagasa et al.[22] showed histological Grade IIb or better. In the present study, the histopathological effect of preoperative administration of CDDP at a mean dose of 174.6 mg and PEP at a mean dose of 74.3 mg was observed in 15 (48.4%) of the 31 patients, higher than the rates in these earlier reports. Kurita et al.[23] administered the combination therapy of CDDP and PEP as preoperative induction chemotherapy in patients with carcinoma of the head and neck, with histopathological effect in four (33.3%) of 12 patients. For cancer of the tongue in particular, a histopathological response rate as high as 57.6% (2/3) was observed by the combined administration of CDDP at a mean dose of 236.7 mg and PEP at a mean dose of 150 mg. The higher rate was probably because the doses of CDDP and PEP were higher than those administered in the present study.

Although the histopathological effect decreased slightly as the clinical stage progressed, there was no significant difference between histopathological effects and clinical stages. With regard to the invasive Grade, it has been shown that the effect of BLM therapy was good in patients with invasive Grades 1 or 2, and that the therapy became increasingly ineffective with progression to invasive Grades 4C and 4D.[12] There have been no reports on the histopathological effects of CDDP from the perspective of an invasive Grade, but the histopathological response rate was as high as 90.0% in patients with invasive Grade 1 or 2 in the present study. However, the rates in patients with invasive Grades 3 and 4C were 41.7% and 16.7%, respectively, and the therapy was not histopathologically effective in any of the patients with invasive Grade 4D. In other words, the histopathological effect significantly decreased as the invasive Grade increased. These results suggest that a tumor's invasive Grade is more closely related to the histopathological effect of combined chemotherapy with CDDP and PEP than its localized size.

With regard to the relationship between clinical and histopathological effects, it seemed that histopathologically ineffective patients were clinically ineffective as well. However, the clinical effect was not necessarily consistent with the histopathological effect in the patient groups showing PR and CR. Up to now, one CR patient with post-chemotherapeutic histological Grade IIa is fairly well, due to a total resection of the tongue after chemotherapy. Our results raise an

important problem regarding the evaluation of clinical effects in the future.

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