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Retrospective Investigation of Cutaneous Squamous Cell Carcinoma on the Lip Treated with Peplomycin Administered Through a Superficial Temporal Artery

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Abstract. *Background: Continuous intra-arterial (IA) administration of peplomycin (PEP) through a tumor-feeding artery is one of the most effective treatments for cutaneous squamous cell carcinoma (cSCC) in cosmetic areas. Patients and Methods: In order to determine the effective and safe dose of PEP and the curative rate of IA-PEP, we retrospectively investigated a case series of 24 patients with cSCC on the lips who were treated with IA-PEP. Results: IA-PEP reduced the tumor mass in all 24 cases (100%). A complete response occurred in 17 patients (70.8%), and a partial response occurred in seven (29.2%). Moreover, 17 patients (70.8%) were cured, three patients developed cervical lymph node metastasis (12.5%), and four developed local recurrence (16.7%). Three out of the 24 patients developed interstitial pneumonia (12.5%). Conclusion: Low-dose IA-PEP administered through a superficial temporal artery was a highly effective treatment that achieved a curative response for 70.8% of patients with cSCC on the lips.*

Cutaneous squamous cell carcinoma (cSCC) is the second most common type of non-melanoma skin cancer (1). Treatment for cSCC is surgical excision or local radiation for conventional cases (2). With advanced tumors and tumors in cosmetic areas, the management of cSCC is determined on a case-by-case basis (1, 3). Among the therapeutic options, chemotherapy is used for the treatment of inoperable cSCC (2, 4). Alter *et al*. reviewed the therapeutic effects of epidermal growth factor receptor inhibitors, such as cetuximab, for the treatment of advanced cSCC, but the 5-year tumor-free rate (cured patients) was not reported (2). More recently, Magrini *et al*. reported that cetuximab is more effective than cisplatin for the treatment of advanced cSCC in combination with radiotherapy (5). They concluded that the 3-year overall survival rate is significantly higher in patients with cSCC treated with cetuximab and radiotherapy compared to those treated with cisplatin and radiotherapy. Since drug tolerance is sometimes induced in molecular-targeted therapy (6), the induction of an antitumor immune response is important for the long-term response in patients with cancer (7).

With regard to conventional chemotherapy for cSCC in cosmetic areas, Edwards *et al*. reported the therapeutic effect of intralesional injection of interferon alpha-2b, which achieved a high percentage of excellent cosmetic results (93.9%) (4). DeConti also reviewed chemotherapy for cSCC and reported the efficacy of several combination preoperative chemotherapies (1). The overall response rate of patient to preoperative chemotherapy using cisplatin and bleomycin was 80%, and the objective response rate to combination therapy using cisplatin, 5-fluorouracil and bleomycin was 84.6% (1). Although various combination therapies for cSCC have been reported, case series of monotherapies for cSCC are limited, and the curative rates of these treatments are unknown (1, 2). We previously reported that even a single administration of peplomycin (PEP) was useful for the treatment of SCC in a small case series and that increased numbers of cytotoxic T-cells are a possible mechanism for the long-term antitumor effects of this monotherapy (8). Our previous study suggested that antitumor immune responses are induced by the intra-arterial administration of PEP, leading to long-term antitumor responses. In the present

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report, we further retrospectively investigated the efficacy of PEP continuously administered through a superficial temporal artery for the treatment of cSCC on the lip and evaluated the curative rate of this monotherapy.

Patients and Methods

Patients. We reviewed a retrospectively collected database of the Department of Dermatology, Tohoku University Graduate School of Medicine, to identify 24 patients with cSCC on the lips that had been treated with intra-arterial administration of PEP through a superficial temporal artery by using an intravascular indwelling catheter from April 1997 through March 2011 (Table I). All patients gave their written informed consent. The study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, Sendai, Japan (2015-1-491).

Indigo carmine was used to place an indwelling catheter into the facial artery, which is the branch of the superficial temporal artery that fed the tumor (8), and 5 mg per day of PEP was continuously administered through the catheter (Figure 1). Patients were staged according to the criteria of the Union for International Cancer Control classification system (9).

Treatment schedule. Before the administration of PEP, we used computed tomography to screen for possible internal malignancies and interstitial pneumonia in all 24 patients but found none. We then performed continuous intra-arterial administration of PEP through a superficial temporal artery, continuously administering 5 mg per day of PEP for 10 to 12 days through the facial artery. If the patient was suspected of developing severe side-effects, such as interstitial pneumonia or embolization of the catheter, we immediately stopped the administration of peplomycin. Subsequently, we observed the tumor mass for 6 weeks. If tumors were macroscopically and histologically absent, the patients were considered to have a complete response (CR). If tumors remained, patients were considered to have a partial response (PR), and the remaining tumors were excised. A representative case of a patient with cSCC treated with intra-arterial administration of PEP through a superficial temporal artery is shown in Figure 2A-E, and a representative case of surgical treatment of cSCC on the lip is shown in Figure 2F-H.

Response assessment. All patients were followed for at least 5 years. We screened for possible local recurrence with a regular physical examination every 3 months for 5 years (Table II). We screened for possible lymph node metastasis and remote metastasis with a computed tomographic scan once a year for 5 years. Subsequently, 5 years after the administration of peplomycin, if no tumors were present, we regarded these patients as cured.

Statistical methods. Tumor response and side-effect rate, and their 95% confidence interval (CI) were estimated.

Results

Demographic data. Patient demographic data are shown in Table I. The patients consisted of 18 men and 6 women with an average age of 72.3 years In all cases, tumors were located on the lower lips. Fifteen cases were stage I, and nine were stage II. Histologically, 11 cases were well-differentiated SCC, 11 were moderately differentiated SCC, and two were poorly differentiated SCC.

Table I. *Patient demographic data, tumor stage, and histological subtype*.

Case	Age, years	Gender	Location	TMN	Stage	Histology
1	88	M	Lower lip	T1N0M0	I	WD
2	81	M	Lower lip	T2N0M0	II	MD
3	70	F	Lower lip	T1N0M0	I	WD
4	70	M	Lower lip	T1N0M0	I	MD
5	59	M	Lower lip	T2N0M0	II	MD
6	66	M	Lower lip	T2N0M0	II	PD
7	61	F	Lower lip	T1N0M0	I	WD
8	62	M	Lower lip	T1N0M0	I	MD
9	64	M	Lower lip	T1N0M0	I	MD
10	71	M	Lower lip	T2N0M0	II	MD
11	75	M	Lower lip	T2N0M0	II	PD
12	79	M	Lower lip	T2N0M0	II	MD
13	88	M	Lower lip	T3N0M0	II	WD
14	59	M	Lower lip	T3N0M0	II	MD
15	69	F	Lower lip	T1N0M0	I	MD
16	81	F	Lower lip	T1N0M0	I	WD
17	72	M	Lower lip	T1N0M0	I	WD
18	67	M	Lower lip	T1N0M0	I	WD
19	77	F	Lower lip	T1N0M0	I	WD
20	73	M	Lower lip	T1N0M0	I	MD
21	75	M	Lower lip	T1N0M0	I	WD
22	62	M	Lower lip	T1N0M0	I	MD
23	87	M	Lower lip	T3N0M0	II	WD
24	79	F	Lower lip	T1N0M0	I	WD

M: Male; F: female; WD: well-differentiated; MD: moderately differentiated; PD: poorly differentiated.

Efficacy of administration of PEP. Twenty-one out of the 24 patients received a complete treatment course of PEP (87.5%; 95% CI=0-175.0%). In three patients (12.5%; 95% CI=0-25.0%), the administration of PEP was stopped due to adverse events. In all 24 cases (100%), the tumor size was reduced by intra-arterial administration of PEP. Case 1 is shown as a representative case in Figure 2. Six weeks after the administration of PEP, we evaluated the tumor histologically and macroscopically. In 17 cases, the SCC tumor mass was completely absent (70.8%; 95% CI=0-141.6%), and in seven cases (29.2%; 95% CI=0-58.4%), some tumor mass persisted and was excised. Among our 24 patients, 17 patients (70.8%; 95% CI=0-141.6%) were cured (5 years tumor-free), three patients developed cervical lymph node metastasis (12.5%; 95% CI=0-25.0%), and four developed local recurrence (16.7%; 95% CI=0-33.4%).

Side-effects. Among the 24 patients, three developed interstitial pneumonia (12.5%; 95% CI=0-25.0%). There were no other grade 3-5 side-effects.

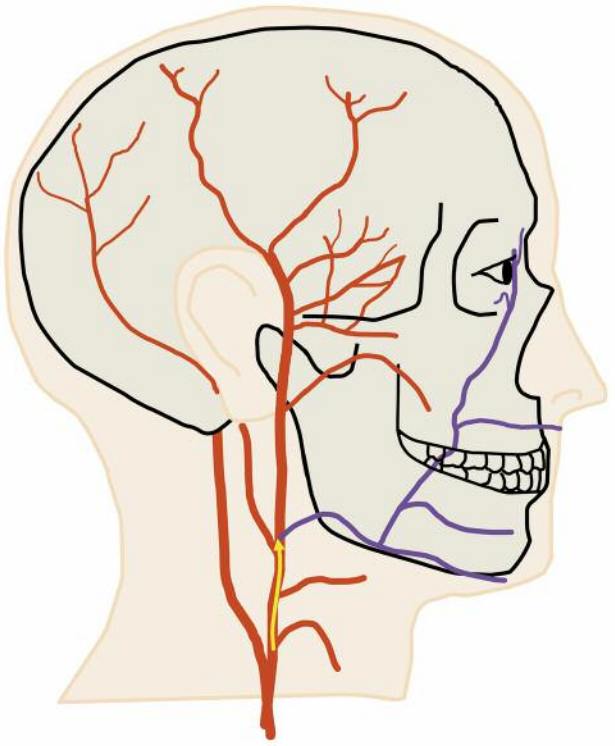

Figure 1. *Schema of intra-arterial administration of peplomycin through a superficial temporal artery. We placed the indwelling catheter into the facial artery (yellow arrow), which is a branch of the superficial temporal artery.We then continuously administered 5 mg peplomycin per day (purple line).*

Discussion

PEP is a bleomycin derivative antibiotic that is used as preoperative chemotherapy for SCC in Japan (10-12). The total dose for conventionally administered PEP ranges from 20 to 110 mg by bolus injection of 5-10 mg/day (10, 11). The dose of PEP is limited due to dose-dependent fatal side-effects, such as interstitial pneumonia (10-12). Therefore, in order to achieve a high concentration of PEP only in the tumor site, we selected continuous intra-arterial administration of PEP through a superficial temporal artery for the treatment of cSCC (8, 13). In addition, as we previously reported, continuous intra-arterial administration of PEP increased the number of cytotoxic T-cells in the tumor site of cSCC, suggesting that this monotherapy might be suitable for the induction of a long-term anti-tumor response through the host immune system. Accordingly, in the present report, we investigated the efficacy of PEP continuously administered through a superficial temporal artery for the treatment of cSCC on the lip, and retrospectively evaluated the curative rate of this monotherapy.

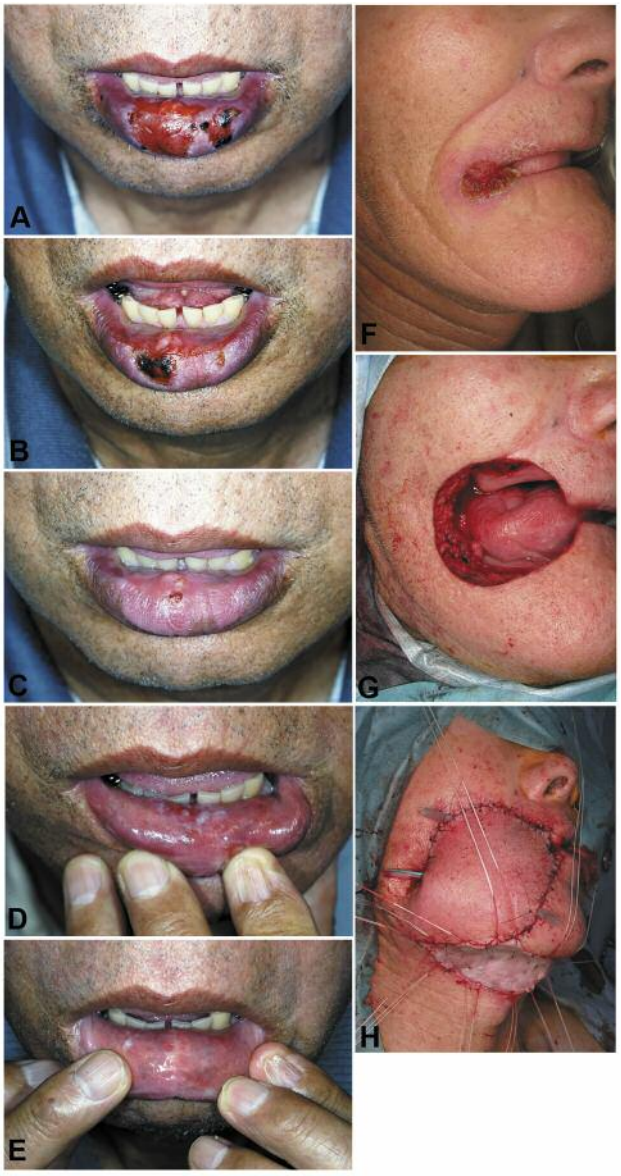

Figure 2. *Cutaneous squamous cell carcinoma (SCC) on the lip treated with continuous intra-arterial administration of peplomycin (A-E) or conventional surgery (F-H). Appearance of case 1 at day 0 (A), 7 (B), 21 (C), 56 (D) and 84 (E) after completion of continuous, intra-arterial administration of 5 mg per day for cutaneous SCC of the lip. Case of cutaneous SCC treated with conventional surgical methods: before treatment (F), radical excision (G), and reconstruction by skin-flap (H).*

In our present study, intra-arterial administration of PEP dramatically reduced the tumor mass in all 24 cases of cSCC on the lip. Notably, with conventional surgical methods, radical excision and skin-flap is mandatory in treating cSCC on the lip, as shown in Figure 2F-H. On the other hand, only inconspicuous scars remained after treatment with

Table II. *Patient demographic data, dose of peplomycin, response evaluation, prognosis, and side-effects.*

Case	Age, years	Dose	Response	Prognosis	Side-effect	Resection
1	88	50 mg	PR	5 Years tumor-free	-	2M
2	81	50 mg	CR	5 Years tumor-free	-	-
3	70	60 mg	CR	5 Years tumor-free	-	-
4	70	37.5 mg	CR	5 Years tumor-free	-	-
5	59	60 mg	CR	Lymph node metastasis	-	-
6	66	60 mg	CR	Local recurrence	-	-
7	61	60 mg	CR	5 Years tumor-free	-	-
8	62	55 mg	CR	5 Years tumor-free	-	-
9	64	50 mg	CR	5 Years tumor-free	-	-
10	71	50 mg	CR	Local recurrence	-	-
11	75	30 mg	CR	5 Years tumor-free	-	-
12	79	60 mg	CR	5 Years tumor-free	-	-
13	88	50 mg	CR	5 Years tumor-free	-	-
14	59	50 mg	CR	Local recurrence	-	-
15	69	50 mg	CR	5 Years tumor-free	-	-
16	81	60 mg	PR	5 Years tumor-free	-	2M
17	72	60 mg	CR	Local recurrence	-	-
18	67	60 mg	PR	5 Years tumor-free	-	2M
19	77	60 mg	PR	5 Years tumor-free	Interstitial pneumonia	2M
20	73	60 mg	CR	5 Years tumor-free	-	-
21	75	60 mg	CR	5 Years tumor-free	Interstitial pneumonia	-
22	62	60 mg	PR	Lymph node metastasis	-	1M
23	87	60 mg	PR	Lymph node metastasis	-	2M
24	79	20.5 mg	PR	5 Years tumor-free	Interstitial pneumonia	1M

CR: Complete response; PR: partial response; M: month.

continuous intra-arterial administration of PEP (Figure 2A-E). At least in terms of cosmetic results, continuous intra-arterial administration of PEP is useful for the treatment of cSCC on the lip. Concerning the patient tolerance of this method, 21 out of the 24 patients received a complete course of PEP (87.5%; 95% CI=0-175.0%). All three patients who did not receive a complete course were cured (tumor-free for 5 years) by subsequent surgical resection. Of the 21 patients that received more than 50 mg of PEP, 14 patients were cured (66.7%; 95% CI=0-133.4%). Concerning the initial tumor response rate, among the 17 cured patients, 12 patients had achieved CR (70.6%; 95% CI=0-141.2%), and five had achieved PR (29.4%; 95% CI=0-58.8%), whereas among the seven patients who experienced relapse, five had achieved CR (71.4%; 95% CI=0-142.8%) and 2 patients had achieved PR (28.6%; 95% CI=0-57.2%). The administration of PEP was stopped in three cases (12.5%; 95% CI=0-25.0%) due to adverse events. These data suggest that intra-arterial administration of PEP through a superficial temporal artery was effective for cSCC on the lips even at a low dose.

Concerning the three patients who developed interstitial pneumonia, one had achieved CR (33.3%), and all three were cured (100%). Among the 21 patients without interstitial pneumonia, 16 patients (76.2%; 95% CI=0-152.4%) achieved CR, five (23.8%; 95% CI=0-47.6%) achieved PR, and 14 patients (66.7%; 95% CI=0-133.4%) were cured. The occurrence rate of interstitial pneumonia was low (12.5%; 95% CI=0-25.0%), and the patients that developed interstitial pneumonia had a good response to intra-arterial PEP therapy. Notably, several experimental reports have suggested that bleomycin-induced lung injury might be enhanced by the reduction of regulatory T-cells (Tregs) in the circulation (14-17). For example, Nemoto *et al*. reported the protective effect of Tregs and acceleration effects of type 1 helper cells, and type 17 helper cells,on bleomycin-induced lung injury in a mouse model (16). On the other hand, several clinical reports have suggested the contribution of tumor-infiltrating forkhead box P3-positive Tregs on the establishment and progression of tumor (18-21). Notably, as we previously reported, intra-arterial administration of PEP reduced the ratio of Tregs among tumor-infiltrating leukocytes (8), which further suggests that PEP might systemically reduce Tregs and promote interstitial pneumonia. Our present cases and these previous reports suggest the possible correlation between the induction of an antitumor immune response and the occurrence of interstitial pneumonia by the administration of PEP. Since we did not assess the ratio of Tregs in peripheral blood in the present study, further studies are needed to test our hypothesis.

In the present report, we describe a case series of 24 patients with cSCC who were successfully treated with

continuous intra-arterial administration of PEP through a superficial temporal artery. Our present data suggest that such therapy is effective for cSCC on the lips, even at a low dose, and that interstitial pneumonia occurred without dose dependency. Our data suggest that although intra-arterial administration of PEP is one of the most effective treatments for cSCC in cosmetic areas, dermato-oncologists should take into account the occurrence of interstitial pneumonia even with use of a low dose of PEP.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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Ethics Approval

This study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, Sendai, Japan (2015-1-491).

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