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ORIGINAL ARTICLE

Platinum and anthracycline therapy for advanced cutaneous squamous cell carcinoma

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Abstract
Background Because metastatic cutaneous squamous cell carcinoma (CSCC) is rare, standard chemotherapy has not been fully established. In Japan, combination platinum and anthracycline chemotherapy has been used for elderly patients with advanced CSCC because of its low toxicity. However, the clinical benefit of this therapy has not been fully examined.
Methods We retrospectively examined the response rate of combination platinum and anthracycline chemotherapy for metastatic CSCC.
Results Eight patients received combination chemotherapy for metastatic lesions; there were lymph node lesions in 6 patients and skin and lung lesions in one patient each. The combination regimens were as follows: cisplatin (CDDP) (60–90 mg/m^2/day, day 1) and adriamycin (ADM) (20–40 mg/m^2/day, day 1 or 2) was administered in 5 patients; CDDP (10–15 mg/m^2/day, days 1–5) and epirubicin (epi-ADM) (10–15 mg/m^2/day, days 1–5) was administered in 2 patients; and carboplatin (CBDCA) (200–400 mg/m^2/day, day 1) and ADM (20–40 mg/m^2/day, day 1 or 2) was administered in one patient. The responses were as follows: complete response in 2 patients (CDDP + ADM for lung metastasis, CDDP + epi-ADM for lymph node metastasis), partial response in 1 (CDDP + ADM for lymph node metastasis), stable disease in 2, and progressive disease in 3. A durable response was observed in 2 patients showing complete responses (58 and 112 months).
Conclusions The clinical effect of the combination of platinum and anthracycline for metastatic CSCC was limited despite the findings of two patients showing durable complete responses.

Keywords Chemotherapy · Cutaneous squamous cell carcinoma · Skin cancer · Platinum · Anthracycline

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Introduction

Because metastatic cutaneous squamous cell carcinoma (CSCC) is rare, the chemotherapy regimens for this condition are limited [1]. Clinical trials of single-agent chemotherapy with peplomycin, irinotecan hydrochloride, fluorouracil, and gefitinib have been performed [2–5]. In combination therapy, the clinical effects of cisplatin (CDDP)-based chemotherapies and the combination of 13-cis-retinoic acid and interferon alfa have been reported [6–11]. Among these, the combination of CDDP and an anthracycline showed a relatively high response rate [58.3 %: complete response (CR) 33.3 %; partial response (PR) 25 %] in the study by Guthrie et al. [6]; the authors mentioned that this regimen might be especially useful for elderly patients because its toxicity was relatively mild. Based on that report, this regimen has been recommended in the Japanese *Guidelines for proper use of antineoplastic agents* [12] and has been frequently used for patients with metastatic CSCC. However, the evidence was reported over a period of more than 20 years ago, and the effectiveness of this

Table 1 Profiles of the patients

	Age (years)/sex	Target lesions	Response	Duration of response (months)	Regimen (number of courses)
1	75/M	LN (mediastinum, axilla)	PD		C[a]A (1)
2	80/M	LN (head and neck)	SD		CA (2)
3	49/M	Skin	SD		CA (3)
4	61/M	Lung	CR	58	CA (4)
5	75/M	LN (axilla, inguinal)	PR	1	CA (2)
6	68/M	Primary (recurrence), LN (axilla, clavicle), pleura	PD		C′[b]A (2)
7	77/M	LN (pelvis)	PD		CA′[c] (2)
8	76/M	LN (axilla, clavicle)	CR	112	CA′ (6)

LN lymph node(s), *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

[a] CA: cisplatin + adriamycin

[b] C′: carboplatin

[c] A′: epirubicin

therapy was examined only for primary lesions but not for metastatic lesions. So we retrospectively examined the response rate for the platinum and anthracycline combination chemotherapy for metastatic lesions of CSCC.

Patients, materials, and methods

The data of patients with advanced CSCC who received combination platinum and anthracycline chemotherapy were retrospectively collected from the records of Shinshu University Hospital from 1995 to 2009. Tumor responses were determined using the Response Evaluation Criteria in Solid Tumors (RECIST), and toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. The RECIST are as follows: complete response (CR), disappearance of all target lesions; partial response (PR), at least a 30 % decrease in the sum of the longest diameters (LDs) for all target lesions; stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum of the LDs from the start of treatment; PD, at least a 20 % increase in the sum of the LDs of target lesions, taking as reference the smallest sum of the LDs recorded from the start of treatment, or the appearance of one or more new lesions.

Results

Eight patients received platinum and anthracycline-based chemotherapy. The patients' profiles are shown in Table 1. The regimens were as follows: CDDP (60–90 mg/m^2/day, day 1) and adriamycin (ADM) (20–40 mg/m^2/day, day 1 or 2) was administered in 5 patients, CDDP (10–15 mg/m^2/day, days 1–5) and epirubicin (epi-ADM) (10–15 mg/m^2/day, days 1–5) was administered in 2patients, and carboplatin (CBDCA) (200–400 mg/m^2/day, day 1) and ADM (20–40 mg/m^2/day, day 1 or 2) was administered in one patient.

The responses were as follows: CR in 2 patients (CDDP + ADM for lung metastasis, CDDP + epi-ADM for lymph node metastasis) (Fig. 1), PR in 1 (CDDP + ADM for lymph node metastasis), SD in 2, and PD in 3 (Table 1). The overall response rate was 37.5 %. The disease-free survival periods of the 2 complete responders were 58 and 112 months, respectively. Neutropenia (grade 3, 1; grade 4, 3), thrombocytopenia (grade 3, 1; grade 4, 1), and anorexia (grade 3, 1) were observed (Table 2).

Discussion

In this study, the response rate of the combination platinum and anthracycline chemotherapy for metastatic CSCC was 37.5 %, including 2 CRs and 1 PR. CSCC and its in situ lesions are the most commonly diagnosed malignant skin neoplasms in Japanese individuals, and the number of patients has gradually increased [13]. The vast majority of patients can be successfully managed with simple surgical excision. Metastasis is rare, and the rate was reported to range from 2.3 to 9.9 % in studies done within the past two decades [14, 15]. In the present data from our hospital, the rate of metastasis in regional lymph nodes was 5 % and that of distant metastasis was 1 % at

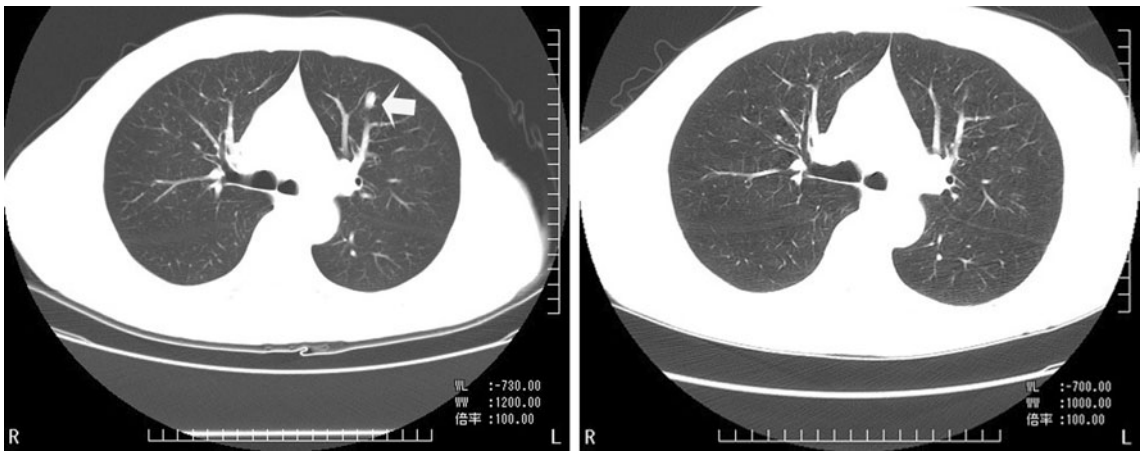

Fig. 1 Computed tomography (CT) scans of of Case 4, a 61-year-old Japanese man with lung metastasis (*arrow*) after the resection of axillary lymph node metastasis and primary squamous cell carcinoma in the chest and postoperative radiation (*left*). After 4 courses of cisplatin and adriamycin chemotherapy, the pulmonary metastases had disappeared (*right*)

Table 2 Toxicities

Adverse event/ grade	1	2	3	4
Neutropenia			1	3
Anemia		2		
Thrombocytopenia			1	1
Nausea	2			
Anorexia	1	5	1	
Weight loss		1		

initial diagnosis. Late metastasis after the initial therapy occurred in 5 % of the remaining patients. The sites of recurrence in the majority of patients were local or regional metastasis, which can be adequately managed with surgical or radiotherapeutic techniques. Accordingly, two-thirds of the patients can survive disease-free [15]. Thus, the use of systemic therapy is limited to patients with distant metastases or locally advanced disease. Because of this situation, studies of systemic therapy including chemotherapy for advanced CSCC have been limited, and the size of these studies has been small (Table 3). In one of these studies, reported by Guthrie et al., the combination of platinum and an anthracycline showed a relatively high response rate (58.3 %; CR 33.3 %, PR 25 %), and the toxicity of the combination was relatively mild [6]. Based on that report, the regimen used in that study was recommended in the Japanese Guidelines for proper use of antineoplastic agents [12], and later, the *General rules for clinical and pathological studies on malignant neoplasms of the skin, 2nd edn* issued by The Japanese Skin Cancer Society [16], and it has been used frequently, together with peplomycin sulfate and irinotecan hydrochloride, for patients with metastatic CSCC. However, the response rate of the platinum and anthracycline combination reported by Guthrie et al. [6] was only for primary lesions, and the clinical effect of this regimen on metastatic lesions has not been examined, except in one Japanese report in 1997 [8]. Although the number of patients in our study was small, it is difficult to perform a study with a large number of patients because of the rarity of the disease, as noted above. A nationwide study is necessary to clarify the clinical effects of systemic therapy for advanced CSCC.

In our study, 2 of 3 responders had CRs and showed durable responses (58 and 112 months). Khansur et al. reported that 2 of 3 patients with distant metastasis showed CR with a combination of CDDP and fluorouracil [10]. Platinum-based combination chemotherapy might be preferable for patients with distant metastasis. Most recently, Maubec et al. reported the result of a phase II study of cetuximab, an epidermal growth factor receptor inhibitor, for unresectable CSCC [17]. The overall response rate was 25 % (1 CR + 8 PRs/36). Although the response rate was rather low compared with those of chemotherapy in the previous reports, Maubec et al. noted that the study included more elderly patients (median age 79 years) compared to the previous studies of the existing systemic chemotherapy. We note that multiple-targeted therapies are being developed for other malignancies. There is a need to evaluate their utility for patients with advanced CSCC and

Table 3 Systemic therapy for advanced cutaneous squamous cell carcinoma

Regimen (year)	*n*	Overall response rate % (*n*)	Primary % (*n*)	Lymph node % (*n*)	Visceral % (*n*)
Peplomycin sulfate [2] (1986)	86	61.6 (53/86)	68.5 (50/73)[a]	25 (4/16)[a]	10 (1/10)[a]
13-cRNA[b] + IFN alfa[c] + cisplatin [11] (2002)	35	34 (12/35)	67 (8/12)	25 (3/12)	9 (1/11)
Irinotecan hydrochloride [3] (1993)	33	39.4 (13/33)	38.5 (10/26)	60 (3/5)	33 (1/3)
13-cRNA[b] + IFN[c] alfa [9] (1992)	28	67.9 (19/28)	92.9 (13/14)	66(4/6)	25 (2/8)
Gefitinib [5] (2006)	15	0 (4 SD/15)			
Fluorouracil [4] (2002)	14	14.2 (2/14)	14.2 (2/14)	–	–
Cisplatin + fluorouracil + bleomycin [7] (1990)	13	84.6 (11/13)	84.6 (11/13)	–	–
Cisplatin/carboplatin + adriamycin/epirubicin [8] (1997)	12	41.7 (5/12)	50 (3/6)	40 (2/5)	0 (0/1)
Cisplatin + fluorouracil [10] (1991)	8	85.7 (7/8)	100 (1/1)	66 (2/3)	100 (3/3)
Cisplatin + adriamycin [6] (1990)	7	57.1 (4/7)	57.1 (4/7)	–	–

[a] Response rates were evaluated for each affected organ

[b] 13-cis-retinoic acid

[c] Interferon

to compare such therapies with the existing systemic chemotherapy regimens.

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Conflict of interest The authors declare that they have no conflict of interest.

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