Platinum and anthracycline therapy for advanced cutaneous squamous cell carcinoma

Running head: Platinum and anthracycline therapy for cutaneous SCC

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Abstract

Background Because metastatic cutaneous squamous cell carcinoma (CSCC) is rare, standard chemotherapy has not been fully established. In Japan, the combination chemotherapy of platinum and anthracycline has been used for elderly patients with advanced CSCC because of its lower toxicity. However the clinical benefit of this therapy has not been fully examined.

Methods We retrospectively examined the response rate of the combination chemotherapy of platinum and anthracycline for metastatic CSCC.

Results Eight patients received chemotherapy for metastatic lesions including lymph node lesions in 6 cases 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 cases, CDDP (10-15 mg/m^2/day, days 1-5) and epirubicin (epi-ADM) (10-15 mg/m^2/day, days 1-5) in 2 cases, and carboplatin (CBDCA) (200-400 mg/m^2/day, day 1) and ADM (20-40 mg/m^2/day, day 1 or 2) in one case. The response was as follows: complete response in 2 cases (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. The durable response was observed in 2 cases showing

complete response (58 months and 112 months).

Conclusions The clinical effect of the combination of platinum and anthracycline for metastatic CSCC is limited despite the inclusion of a few cases showing durable complete response.

Mini-Abstract:

The clinical effect of the combination of platinum and anthracycline for metastatic cutaneous squamous cell carcinoma is limited despite the inclusion of a few cases showing durable complete response.

Key words: chemotherapy, cutaneous squamous cell carcinoma, skin cancer, platinum, anthracycline

Introduction

Because metastatic cutaneous squamous cell carcinoma (CSCC) is rare, the regimens of chemotherapy for this condition are limited [1]. In a single agent, clinical trials of pepleomysin, irinotecan hydrochloride, fluorouracil and gefitinib were performed [2 – 5]. In combination therapy, the clinical effects of cisplatin (CDDP)-based chemotherapies and the combination of 13-cis-retinoic acid and ineterferon alfa were reported [6 -11]. Among these, the combination of CDDP and anthracycline showed relatively high response rate (58.3%: complete response (CR), 33.3%; partial response (PR), 25%) [6]. The authors mentioned that this regimen might be especially useful for elderly patients because its toxicity was relatively mild. Based on this report, this regimen was recommended in the guidelines of Japan **issued by The Japanese Skin Cancer Society** and has been frequently used for patients with metastatic CSCC [12]. However, the evidence was reported over more than two decades, and the effectiveness of this therapy was examined only for primary lesions but not for metastatic lesions. So, we retrospectively examined the response rate for the combination chemotherapy of platinum and anthracycline for metastatic lesions of CSCC.

Materials and Methods

The data of patients with advanced CSCC who were treated with combination chemotherapy of platinum and anthoracycline were retrospectively collected from the list of Shinshu University Hospital from 1995 to 2009. Tumor responses were determined using **Response Evaluation Criteria In Solid Tumors (RECIST)** criteria and toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. **The response criteria by RECIST is as follow; Complete Response (CR): Disappearance of all target lesions, Partial Response (PR): At least a 30% decrease a sum of the longest diameter (LD) for all target lesions, Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started, Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions**

Results

Eight patients were treated with 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 cases, CDDP (10-15 mg/m^2/day, days 1-5) and epirubicin (epi-ADM) (10-15 mg/m^2/day, days 1-5) in 2 cases, and carboplatin (CBDCA) (200-400 mg/m^2/day, day 1) and ADM (20-40 mg/m^2/day, day 1 or 2) in one case.

The response was as follows: CR in 2 cases (CDDP+ADM for lung metastasis, CDDP+epi-ADM for lymph node metastasis) (figure), PR in 1 (CDDP+ADM for lymph nodes 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 months 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

The result showed that the response rate of the combination chemotherapy of platinum and anthracycline for metastatic CSCC was 37.5% including 2 CR and 1 PR. CSCC and its in situ lesion 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 be from 2.3 to 9.9% in the studies within

the past two decades [14, 15]. In the data from our hospital, the rate of metastasis in regional lymph nodes was 5% and that of distant metastasis was 1% at initial diagnosis. Late metastasis after 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. 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 these studies, the combination of platinum and anthracycline showed a relatively high response rate (58.3%: CR, 33.3%; PR, 25%), and its toxicity was relatively mild[6]. Based on that report, this regimen was recommended in the guidelines for the management of skin neoplasms issued by The Japanese Skin Cancer Society and has been frequently used as well as peplomycin sulfate and irinotecan hydrochloride for patients with metastatic CSCC [16]. However, the response rate of the combination of platinum and anthracycline in the first report 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 is small, it is difficult to

perform a study with a large number of patients because of the rarity of the disease as described above. A nationwide study is necessary to clarify the clinical effects of systemic therapy for advanced CSCC.

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

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Figure legends

CT 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, the pulmonary metastases disappeared (right).

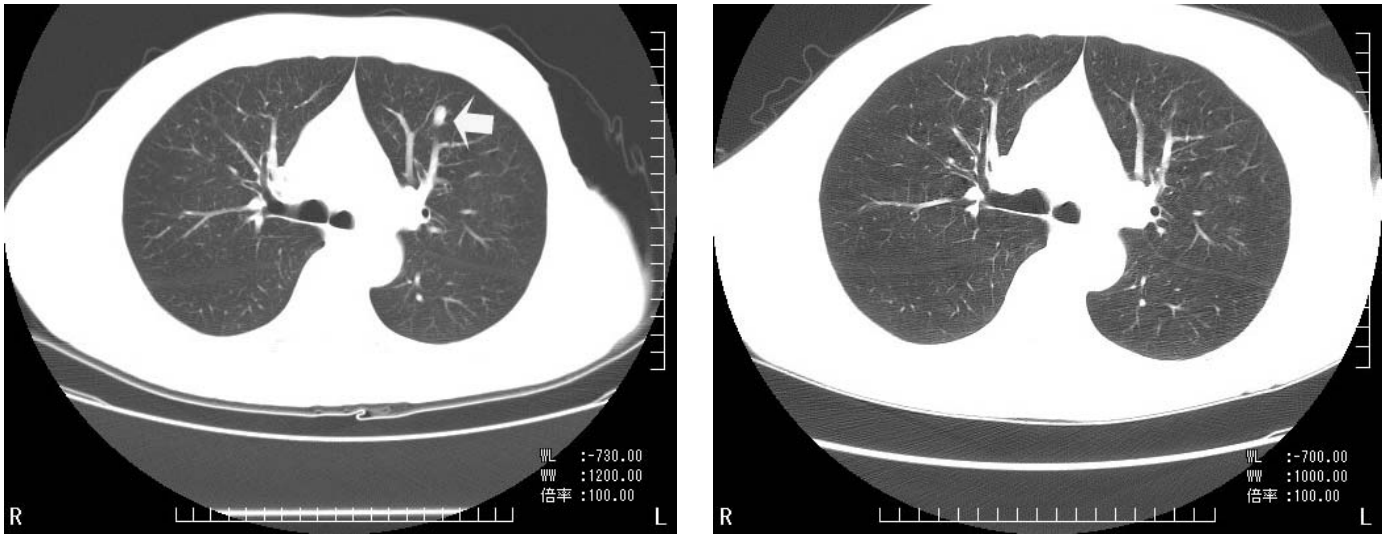

Fig. 1

Table 1 The profiles of the patients

	Age/Sex	Target lesions	Response	Duration of response (month)	Regimen (number)
1	75/M	LN* (mediastinum、axilla)	PD		C †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' ‡A (2)
7	77/M	LN (pelvis)	PD		CA'§ (2)
8	76/M	LN (axilla、clavicle)	CR	112	CA' (6)

*LN: lymph node(s)
†CA: cisplatin + adriamycin
‡C': carboplatin
§A': epirubicin

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		

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)*	25 (4/16)*	10 (1/10)*
13-cRNA† + IFN alfa‡+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† + IFN‡ alfa[9] (1992)	28	67.9 (19/28)	92.9 (13/14)	66(4/6)	25 (2/8)
Gefitinib[5] (2006)	15	0 (4SD/15)			
Fluorouracil[4] (2000)	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 + Adroamycin / 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)	-	-

*: response rates were evaluated each organ.
†: 13-cis-retinoic acid
‡: interferon