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Inhibition of head and neck metastatic and/or recurrent cancer by local administration of multi-cytokine inducer OK-432

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Abstract

The multi-cytokine inducer OK-432 is a pulverized preparation of the low-virulence SU strain of *Streptococcus pyogenes* of human origin. A reduction of the tumour mass in the OK-432-injected areas was observed in 11 out of 13 patients with metastatic and/or recurrent head and neck cancer. Complete response (CR), partial response (PR) and minor response (MR) were noted in six, three and two cases respectively. OK-432 local administration therapy could create a new strategy for cancer therapy.

Key words: Head and neck neoplasms; Chemotherapy; OK-432

Introduction

OK-432 is a pulverized preparation of the low-virulence SU strain of *Streptococcus pyogenes* of human origin, which is treated with heat and penicillin G, followed by lyophilization of the whole mixture (Picibanil, Chugai Pharmaceutical Co., Ltd., Tokyo). Although OK-432 retains several characteristics of the original cells, the lack of growth activity has been confirmed by many different culture systems both *in vivo* and *in vitro*. It readily yields a slightly turbid suspension in saline or any other fluid, such as one per cent lidocaine. One mg of dried powder corresponds to 10 KE of OK-432 (IKE (Klinische Einheit) = 0.1 mg dried *streptoccus pyogenes* = 1×10^8 streptococcal cells OK-432 has been found to be a potent inducer of gamma interferon (IFN-r) (Saito *et al.*, 1982; Wakasugi *et al.*, 1982; Saito *et al.*, 1983) along with bacille de Calmette-Guérin (BCG) and *Corynebacterium parvum*. Further studies have disclosed its ability to induce interleukin 1 (IL-1) (Ichimura *et al.*, 1985), interleukin 2 (IL-2) (Wakasugi *et al*, 1982; Ichimura *et al.*, 1985) and tumour necrosis factor (TNF) (Yamamoto *et al.*, 1986). In concordance with these findings, OK-432 has been shown to augment natural killer (NK) activity in humans and mice (Oshimi *et al.*, 1980a; Uchida and Mickshe, 1983a; Uchida and Mickshe, 1983b), and to induce activated macrophages (Ishii *et al.*, 1976; Saito *et al.*, 1984; Ikeda *et al.*, 1985). Current knowledge of the macrophage-T cell lymphokine cascade indicates that the participation of such lymphokines could be a prerequisite for the appearance of cytotoxic T lymphocyte (CTL).

Based on these findings, the use of OK-432 as a biological response modifier (BRM) for cancer therapy was started in the 1970s. It was given by various routes of administration, including intravenous, intramuscular, subcutaneous, intracutaneous, and intracavitary injection. Many clinical trials at Japanese cancer centres have shown limited efficacy. In 1989, the Japanese Pharmaceutical Society and the Ministry of Welfare finally decided that its usefulness was doubtful (PMS report 1989). Our experience by the systemic administration route had also indicated little efficacy.

Local injection therapy with OK-432 was started fortuitously. In 1985 we treated a patient with a T_{1a} laryngeal squamous cell carcinoma with a series of therapies. After laser surgery there was a recurrence. Following laryngectomy, there was a neck recurrence treated by irradiation. A submental recurrence occurred which was treated by local excision with a positive surgical margin. The local recurrence in the submental space was obvious, thus a treatment plan for the residual cancer had to be planned. Further radiotherapy was unlikely to be effective because of the radio-resistance of this tumour. Re-excision and chemotherapy immediately after local excision could not be recommended because of the patient's poor general condition. Accordingly we selected to undertake local injection of OK-432 into the submental space in light of reports that showed a cytokine-inducing activity. OK-432 injection into his slightly

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TABLE Ia

Cases	Age	Sex	Diagnosis	Pathology	Treatment before OK-432 local injection			Time interval between the end of last treatment and the start of OK-43
					Operation	Irradiation	Chemotherapy	
1.	49	M	Laryngeal Ca.	S.C.C.	+	+	5-FU	4 months
2.	48	F	Oral Ca.	S.C.C.	+	+	5-FU, PEP	2 months
3.	64	M	Laryngeal Ca.	Mucoepider.	+	+	ADM, PEP	2 months
4.	73	F	Tongue Ca.	S.C.C.	+	+	CDDP, 5-FU	4 months
5.	61	M	Ca. of tonsil	S.C.C.	+	+	5-FU	1 month
6.	69	M	Oral Ca.	S.C.C.	+	+	5-FU	6 months
7.	48	M	Maxillary Ca.	S.C.C.	+	+	CDDP, 5-FU	4 months
8.	48	M	Maxillary Ca.	Adeno.	+	+	5-FU	4 months
9.	60	M	Parotid Ca.	Mucoepider.	+	+	5-FU	2 months
10.	63	M	Laryngeal Ca.	S.C.C.	+	+	(–)	2 months
11.	69	M	Hypopha. Ca.	S.C.C.	+	+	5-FU	3 months
12.	43	F	Epipha. Ca.	S.C.C.	+	+	5-FU	10 months
13.	40	F	Maxillary Ca.	S.C.C.	+	+	CDDP, 5-FU	2 months

M: male, F: female, Ca.: carcinoma, S.C.C.: squamous cell carcinoma, Mucoepider.: mucoepidermoid carcinoma, Adeno.: adenocarcinoma, CDDP: cisplatin, 5-FU: 5 fluorouracil, PEP: peplomycin sulfate, ADM: adriamycin.

enlarged submental area was started at a dose of 5 KE once a week and a total of 130 KE was injected into the lesion. One month after the start of treatment the area began to gradually soften and hard scar tissue formed after approximately two years. The patient is still disease-free 10 years from the initiation of treatment.

This case encouraged us to continue local injection therapy with OK-432 for refractory recurrent cancer in spite of radical treatments. The present report covers the clinical concerns and difficulties associated with 13 patients who responded to local administration of OK-432.

Patients and methods

Table Ia outlines the course of treatment for 13 patients with head and neck tumours (three, carcinoma of the larynx; three, carcinoma of the maxillary sinus; two, carcinoma of the oral cavity; one, carcinoma of the tongue; one, parotid carcinoma; two, carcinoma of the pharynx and one, carcinoma of the tonsil). All patients had frequent recurrences despite surgery and radiochemotherapy. The mean age of the patients was 56.5 years with a range of 40 to 73 years. The time intervals between the end of last treatment, radiotherapy and chemotherapy and the start of OK-432 ranged from one month to ten months. OK-432 (Picibanil, Chugai Pharmaceutical Co., Ltd., Tokyo) 0.05–2.0 mg (0.5–20 KE; 1KE = 0.1 mg of dried streptococcal cells) was injected around the tumour mass once a week. To relieve the pain of injection, a one per cent lidocaine solution of OK-432 was used (5 KE/1–5 ml). The injection was performed with the injection machine which we devised from an injector for gingival anaesthesia. Patients were evaluated on the basis of the WHO Handbook for Reporting Results of Cancer Treatment. No other treatment was given to these patients at the same time as OK-432. No patient had received salvage surgery. OK-432 was administered subcutaneously. Only Case 2 received it systemically.

Results

As shown in Table Ib, a distinct reduction of the tumour mass in the areas of OK-432 injection was

TABLE Ib

Cases	Target lesions	Total dose of OK-432	Lesional effect	Total effect	Survival duration after the start of therapy
1.	Submental area	730	CR	CR	120 months, alive
2.	Retromoral area	64.7	CR	CR	16 months, alive
3.	Parietal meta.	300	CR	PR	8.5 months, death by brain meta.
	Neck LM	110	MR		
4.	Tongue (Oral base)	972	CR	CR	15 months, death by lung meta.
5.	Neck rec.	312	PR	PR	5 months, death by rupture of carotis
	Neck LN (on carotis)	200	CR		
	Neck LNs	120	not evaluable		
6.	Neck LN	167	MR	MR	15 months, death by local invasion
7.	Local rec.	75	NC	PR	4 months, death by brain invasion
	Neck LNs	60	PR		
8.	Neck meta.	94	NC	NC	4 months, death by brain invasion
9.	Local rec.	70	PD	PD	4 months, death by local invasion
10.	Neck meta.	150	MR	MR	7 months, death by rupture of carotis
11.	Parotis-Sub-mandibular area	1196.5	CR	CR	43 months, alive
12.	Neck LN	376.5	CR	CR	42 months, alive
13.	Local rec.	70	CR	CR	36 months, alive

LN: lymph node, rec.: recurrence, meta: metastasis, CR: complete response, PR: partial response, MR: minor response, NC: no change, PD: progressive disease.
Case 2: We did not follow up this case because of change of address.

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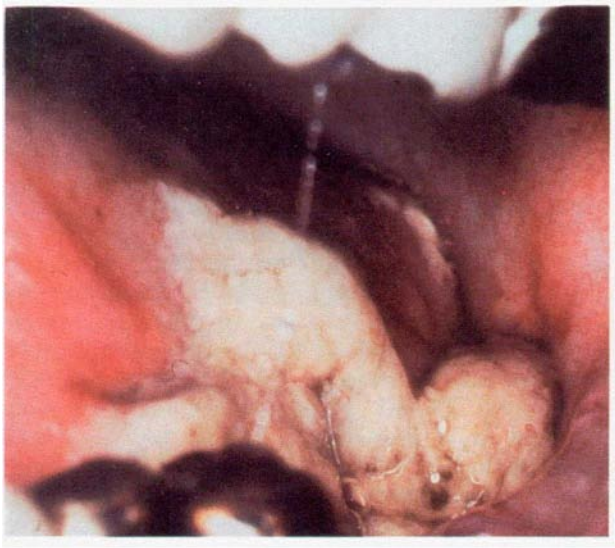

FIG. 1a

(*Case 2*) A tongue-retromolar lesion of a patient with squamous cell carcinoma. After local injection of OK-432 (about 50 KE), the lesion showed a marked necrosis.

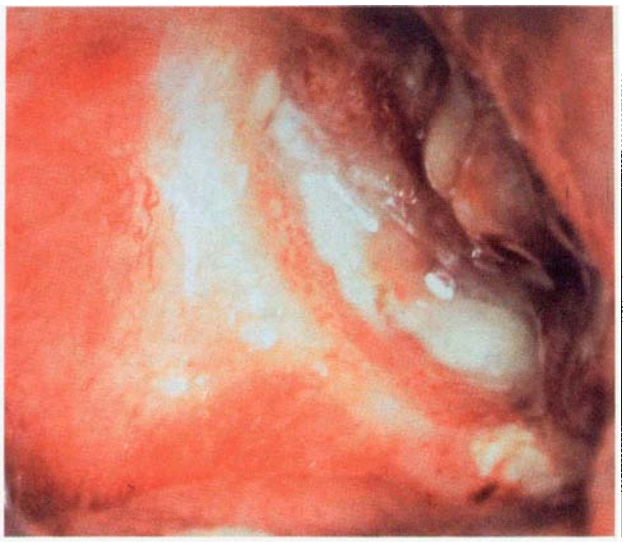

FIG. 1b

Necrosis was so extensive that we were able to see the distinct pulsation of carotid artery.

observed in 11 out of 13 patients with metastatic cancer. From the evaluation in accordance with the WHO Handbook for Reporting Results of Cancer Treatment, a complete response (CR) was seen in six cases, a partial response (PR) was seen in three cases and minor response (MR) was seen in two cases. In addition, no change (NC) was seen in one case and progressive disease (PD) in one case. *Case 1*, which was described in the introduction, was still disease free 10 years from the start of treatment. The duration of response in the other CR cases (*Cases 2, 4, 11, 12* and *13*) were 16, 15, 43, 42 and 36 months respectively.

High-fever (37–39°C), was the most common side effect but was controlled by commonly used anti-pyretics (Indometacin, Diclofenac sodium etc.)

Case reports

The clinical histories of four representative cases are given. *Case 2* presented with a T_1 squamous cell carcinoma of the retro-molar space. After resection by CO_2 laser surgery, recurrence was found at the same area. Despite the radiotherapy, the lesion did not reduce in size. OK-432 local injection therapy for this lesion was started with a dose of 0.2 KE. After 50 KE had been administered, the tumour and the surrounding area showed marked necrosis (Figure 1a). The necrosis was so extensive that we were able to see distinct pulsation of the carotid artery (Figure 1b). Because of the risk of carotid rupture, local injection was converted to systemic administration. This patient has been in remission for over two years after local injection therapy and the lesion has changed into scar tissue.

Case 3 had cervical and parietal metastatic (Figure 2a) lesions of laryngeal carcinoma. Radiotherapy at a dose of 50 Gy was combined with chemotherapy, but the lesion showed little response to radio-chemotherapy. Accordingly, we started OK-432 local injection therapy at the cessation of irradiation. Figure 2b shows the parietal lesion after the injection of 175 KE. After injection of a total 300 KE, OK-432, the lesion showed central necrosis and finally it changed to scar tissue (Figure 2c). The patient, however, died of brain metastasis 8.5 months after the start of OK-432 therapy.

Case 5 represents a patient with cervical metastasis secondary to carcinoma of tonsil. OK-432 injection was used because of a left neck recurrence (Figure 3c). OK-432 was injected directly, in contrast to our usual method in which we inject around the tumour mass. After 50KE was injected, the lesion near the patient's left carotid artery began to soften. At this time, as shown in Figure 3b, this lesion looked enlarged but the duration had changed to soft tissue. We continued to inject OK-432 into this lesion and it developed a marked necrosis (Figure 3c). After about 200KE had been injected into this area the carotid artery beneath the lesion unfortunately ruptured while the patient was at home.

Case 13, the latest case, is a T_3 maxillary carcinoma patient with a positive surgical margin after the radiochemotherapy and surgical resection. OK-432 was directly injected to the buccal lesion through the facial skin. The lesion has been completely controlled for 36 months and several biopsies taken during and after the injection were negative.

Discussion

Purified human Biological response modifiers (BRM) including IFN, IL2 etc. were tested in the 1980s, but were not very successful. One of the immunostimulants OK-432 is also included in the category of a BRM and induces substances such as IFN, IL1, IL2, TNF etc. (Saito *et al.*, 1982; Wakasugi *et al.*, 1982; Saito *et al.*, 1983; Ichimura *et al.*, 1985) and activates cellular immunity (Ishii *et al.*, 1976; Oshimi *et al.*, 1980a; Uchida and Mickshe, 1983a; Uchida and Mickshe, 1983b; Saito *et al.*, 1984; Ikeda *et al.*, 1985; Yamamoto *et al.*, 1986). OK-432 causes

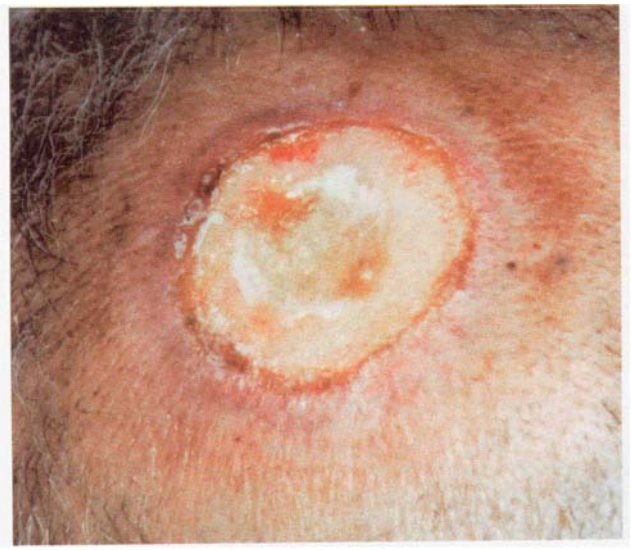

FIG. 2a

(*Case 3*) Parietal metastasis of mucoepidermoid cell carcinoma (before OK-432 local injection).

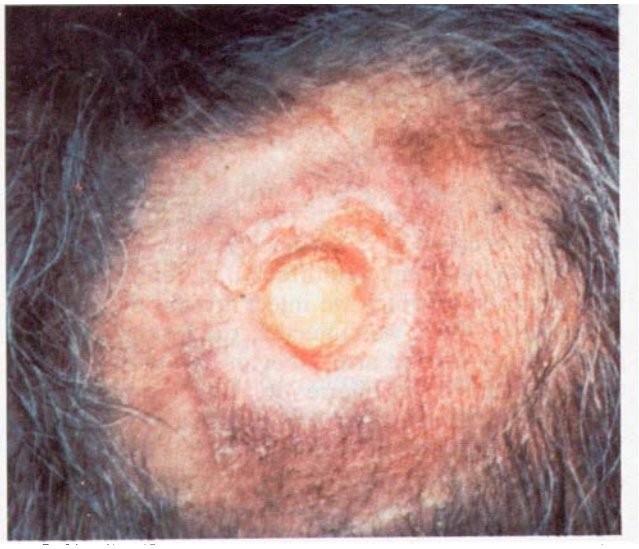

FIG. 2b

After the injection of 175 KE, this lesion showed central necrosis and changed to soft tissue.

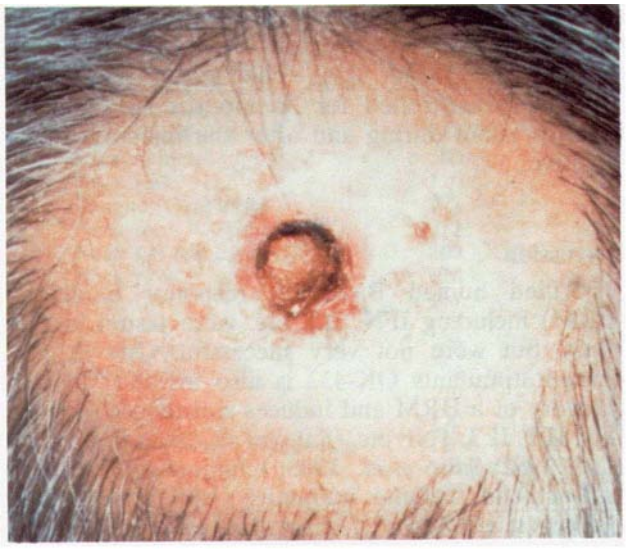

FIG. 2c

After injection of OK-432 (total 300 KE), the lesion finally changed to scar tissue.

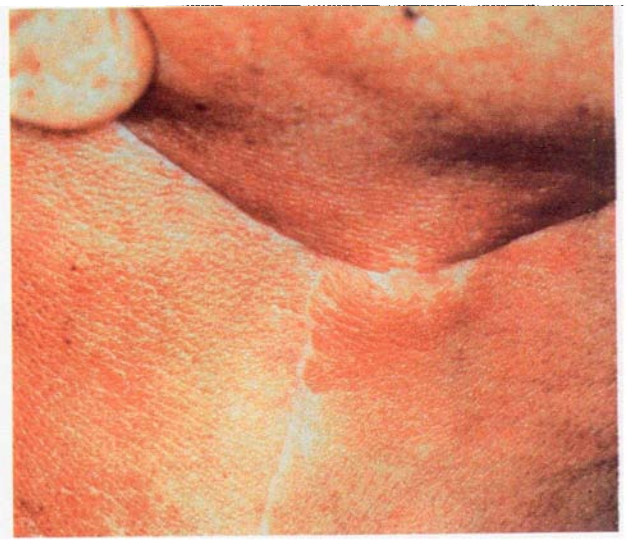

FIG. 3a

(*Case 5*) Cervical metastasis of carcinoma of tonsil was highly suspected after the neck dissection.

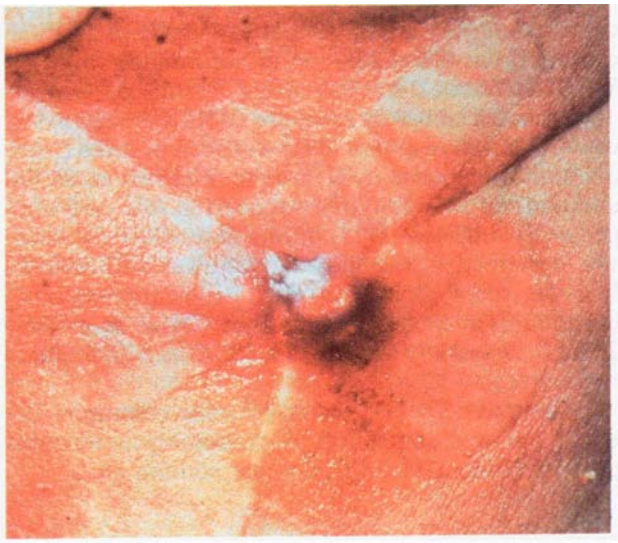

FIG. 3b

After about 50 KE injected, this lesion looked enlarged but the induration had changed to a soft abscess-like tissue.

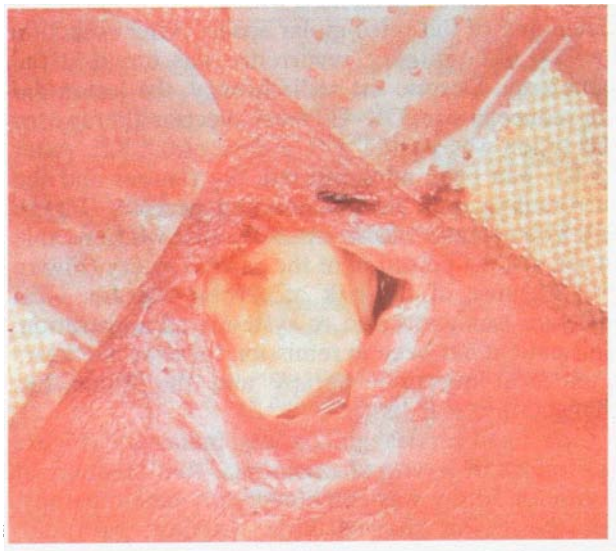

FIG. 3c

We continued to inject OK-432 into this lesion and which showed marked necrosis. After about 200 KE was injected into this area, rapture of the carotid artery beneath this lesion occurred at home, three days later.

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immunopotentiating cells activated by lymphokines to accumulate around the tumour mass. It has been shown in a series of experiments that these cells have a killing effect on cancer cells (Oshimi *et al.*, 1980b; Kokunai *et al.*, 1985; Yamashita *et al.*, 1986; Saito *et al.*, 1988; Kitahara *et al.*, 1989; Hirakawa *et al.*, 1989; Fujimori *et al.*, 1989; Fujioka *et al.*, 1990) and some recent reports noted the contact between OK-432, lymphocytes and tumour cells caused the change of killing-activity, cytokine production and antigen expression (Mizutani *et al.*, 1991; Misaki *et al.*, 1992; Yamaue *et al.*, 1992). Fujimori *et al* (1989) and Fujioka *et al.*, (1990) reported clinical successes when the combined use of OK-432 and rIL-2 improved the results of OK-432 local injection therapy. In addition to the use for malignancy, Ogita *et al.* (1991) reported a surprising effect on a paediatric lymphangioma. The Welfare Ministry approved the use of OK-432 for lymphangioma in 1994. Based on these reports and clinical trials, we should not neglect OK-432's utility as the 'multi-cytokine inducer'.

The augmentation of human immunity by OK-432 was found to be induced at a dose of more than 3 KE and continued for 3-4 days (unpublished data). Considering these findings we are planning a protocol for local administration of OK-432.

Our results (CR6, PR3 out of 13) showed the effect of OK-432 in reducing tumour mass in patients with metastatic and/or recurrent head and neck cancer. OK-432 could create a new strategy for cancer therapy.

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