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EFFECT OF BLEOMYCIN ON BENIGN AND MALIGNANT CUTANEOUS TUMOURS

Yutaka Mishima and Masahiro Matunaka

From the Department of Dermatology, Wakayama Medical University, Wakayama, Japan

Abstract. A new anti-tumour antibiotic called Bleomycin, isolated from Streptomyces verticillus, has been clinically evaluated for the treatment of benign DNA virus tumours and malignant cutaneous neoplasms. We found that the systemic administration of Bleomycin resulted in marked to moderate regression of prickle cell carcinoma, condyloma accuminatum and verruca vulgaris. Although systemic administration of Bleomycin for basal cell epithelioma is reported minimally effective, it is found that the lesion can be eradicated by local injection of this drug.

Bleomycin is a new anti-tumour antibiotic isolated from *Streptomyces verticillus* by Umezawa et al. (6, 7).

This compound has been found to inhibit the synthesis of DNA in the presence of sulfhydryl compounds in E. coli, HeLa cells and Ehrlich cells at concentrations of 40 μg/ml, and at lower concentration to inhibit cell division. Bleomycin has been found to be highly concentrated in the skin of mice $^1/_2$ hour after administration (4).

Exhaustive toxicity tests with mice, rats, rabbits, dogs, and monkeys have demonstrated no serious side effects other than the occasional occurrence of moderate to severe lung congestion and fibrosis (1). Clinical investigations of the effect of Bleomycin on various cutaneous malignant tumours have been carried out at a number of institutions (2, 3).

We report briefly here the effects of systemic and locally administered Bleomycin in prickle cell carcinoma, basal cell epithelioma, reticulum cell sarcoma and benign DNA virus tumours.

PATIENTS AND METHODS

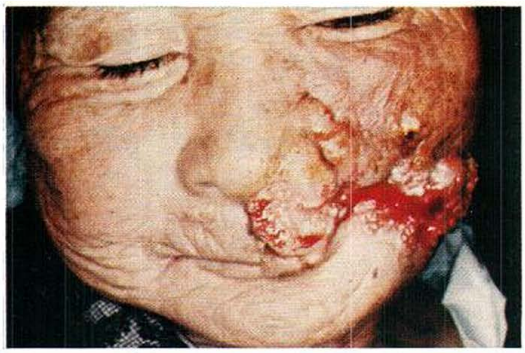
The patients having malignant cutaneous tumours, reported on in this study, comprised 2 cases of squamous cell carcinoma, 3 cases of basal cell epithelioma, and 1 case of reticulum cell sarcoma. All diagnoses of malignant tumours were confirmed by biopsy. Benign DNA virus tumours such as condyloma accuminatum in 1 case and verruca vulgaris in 2 cases are also included in this report. When Bleomycin was administered systemically, the dose was 15 mg injected intravenously twice weekly. Local injection of Bleomycin was carried out daily using 0.2–1.5 mg/ml concentration.

RESULTS AND DISCUSSION

Fig. 1 shows the left cheek of a 66-year-old female exhibiting a fungating, partially ulcerated prickle cell carcinoma prior to the following treatment. She was treated with 100 mg/day cyclophosphamide for 9 weeks (26.12.1967 – 29.2.1968) with no distinct response. Two radiation courses of 25 (6.12.1967 – 19.1.1968) and 36 (7.6.1968 – 19.7.1968) treatments to a total of 12 200 R was administered. The initial response was moderately good but the tumour began to grow again. Thus, therapy with Bleomycin was initiated on August 22nd, 1968. Fig. 2 shows this patient after systemic administration of 450 mg Bleomycin. The patient exhibited complete clinical regression of the cutaneous tumour.

The second case of squamous cell carcinoma was that of an 81-year-old female who developed a grade 4 carcinoma in the right mandibular area. After 105 mg of systemically administered Bleomycin, distinct regression of the tumour was seen. The patient died of cachexia before completion of the full Bleomycin course. Permission for an autopsy was refused.

In contrast to prickle cell carcinoma, systemic administration of Bleomycin for basal cell epithelioma is reported to be minimally effective (2). Furthermore, considering that this tumour is generally only locally invasive, we have employed local injection of Bleomycin. Fig. 3 shows the clinical appearance of a biopsy-confirmed pig-



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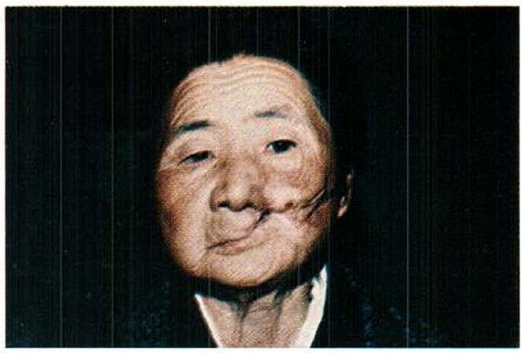

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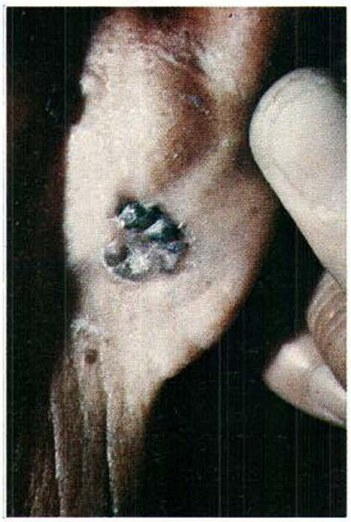

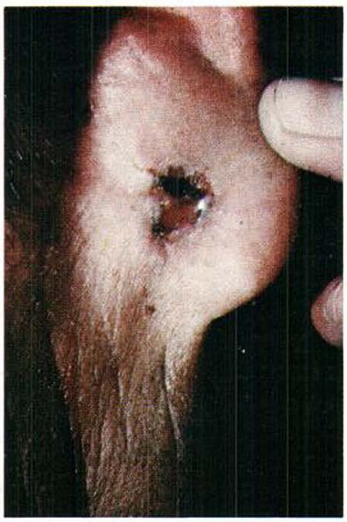

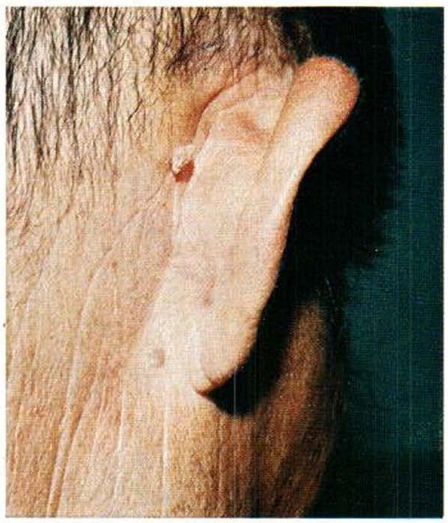

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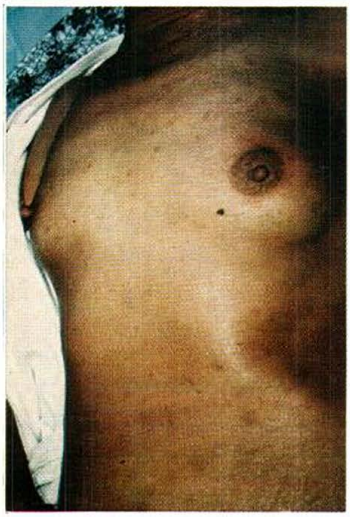

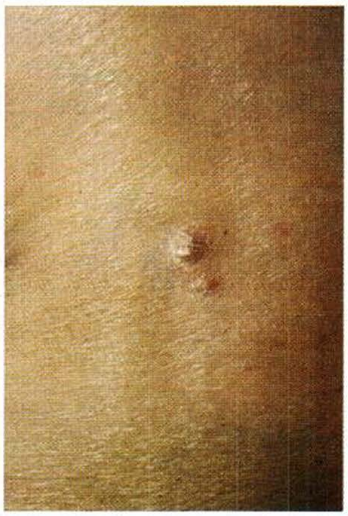

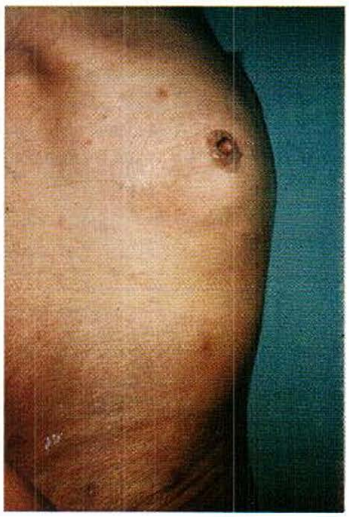

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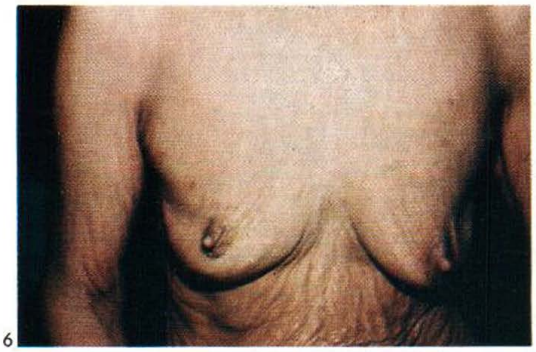
Fig. 1. Fungating partially ulcerated prickle cell carcinoma on the left side of the face of a 66-year-old female prior to Bleomycin and other treatments.

Fig. 2. Regression of prickle cell carcinoma shown in Fig. 1 after systemic administration of 450 mg Bleomycin.

Fig. 3. Pigmented basal cell epithelioma on the back of the ear lobe of a 51-year-old man.

Fig. 4. (*a*) Superficial ulceration resulting from destruction of basal cell epithelioma shown in Fig. 3 after seven local injections of Bleomycin. (*b*) Complete cure resulting in scar formation seen 2 years later.

Fig. 5. (*a*) Multiple half- to full pea-sized subepidermal erythematous nodules of reticulum cell sarcoma on the trunk prior to the treatment. (*b*) Closer view of nodules shown in Fig. 5 *a*. (*c*) A large egg-sized subepidermal nodule of reticulum cell sarcoma on the lateral side of the right breast prior to the treatment.



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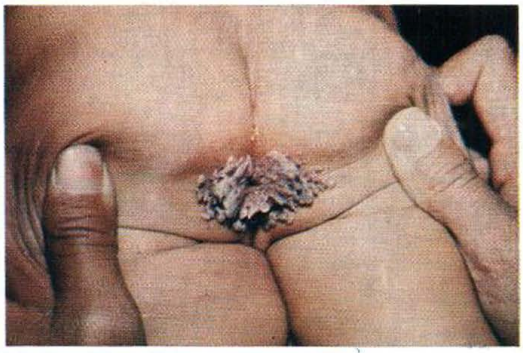

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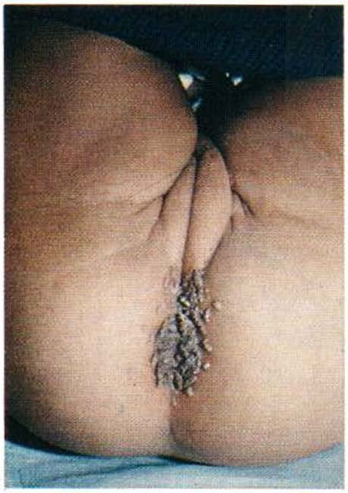

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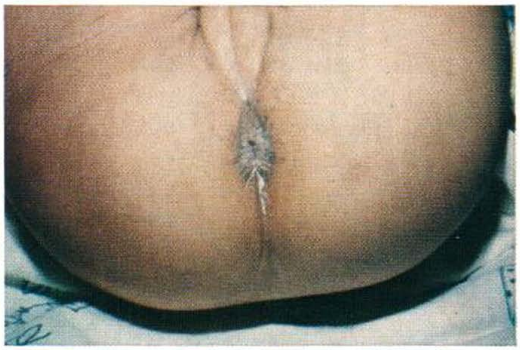

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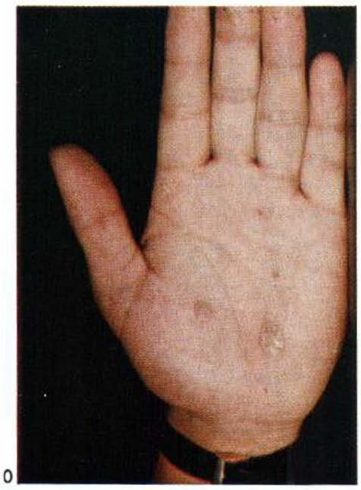

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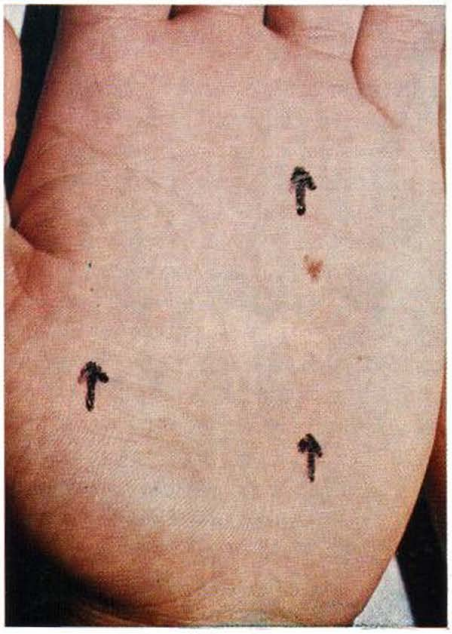

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Fig. 6. Clinical appearance of patient shown in Fig. 5 after Bleomycin treatment exhibiting disappearance of pea-sized nodules and slight regression of egg-sized nodule.
Fig. 7. Condyloma accuminatum in the anal region of a 12-month-old girl prior to Bleomycin treatment.
Fig. 8. Marked regression of the lesion shown in Fig. 7 after only two systemic injections (18 mg) of Bleomycin.
Fig. 9. Complete regression of condyloma accuminatum shown in Figs. 7 and 8 after administration of 93 mg Bleomycin.
Fig. 10. Clinical appearance of verrucae vulgares occurring in a 20-year-old male prior to the treatment.
Fig. 11. Complete regression of verrucae vulgares following systemic injections (30 mg) of Bleomycin.

mented basal cell epithelioma appearing on the back of the ear lobe of a 51-year-old male. After 7 local injections of Bleomycin, the lesion exhibits almost complete destruction, resulting in superficial ulceration (Fig. 4 *a*). After 20 injections there was complete destruction of the tumour cell nests. Six months later the lesion was completely cured, resulting in scar formation and no recurrence is seen 2 years later (Fig. 4 *b*). Further experience in cases such as the following has indicated that the lower concentration of 0.2 mg/ml is often sufficient for therapy in basal cell epithelioma.

Another case of multiple superficial basal cell epitheliomas appearing on the back of a 67-year-old male was treated with local injections of 1–2 ml each, 0.2 mg/ml Bleomycin. After 4 injections there was complete disappearance of the tumour with superficial ulceration. In contrast, local injection of Bleomycin at this concentration caused no ulceration in normal skin. Three months later the lesions were completely healed with mild scar formation. Similar results were obtained in the treatment of the lower eyelid lesion of a 68-year-old female.

Reticulum cell sarcoma occurring in a 63-year-old female (5) was treated with systemically administered Bleomycin. Fig. 5 shows the clinical appearance of this patient before treatment, exhibiting multiple half- to full pea-sized subepidermal firm erythematous nodules (Fig. 5 *a, b*) on the trunk as well as one firm egg-sized nodule (Fig. 5 *c*) on the lateral side of each breast and in the left axillary lymph-node. Biopsy of a pea-sized cutaneous nodule revealed sharply demarcated patches of cellular infiltrates composed of atypical reticulum cells and pleomorphic histiocytes in the upper and mid-corium. Few of these tumour cells had invaded the epidermis.

After the administration of 45 mg Bleomycin intravenously, there was almost complete disappearance of the pea-sized nodules (Fig. 6) and moderate regression of the egg-sized nodules. After 180 mg additional Bleomycin there was complete disappearance of the small cutaneous lesions, but the larger subcutaneous and lymph nodules remained almost unchanged. These subcutaneous non-responding lesions are being treated in combination with 1 600 R superficial X-ray with moderate response, since Bleomycin has been shown to increase radiosensitivity by interfering with the repairing process of radiation damaged DNA (8).

Fig. 7 shows a representative case of condyloma accuminatum occurring in a 12-month-old girl who had had the lesion for 3 months. There was a walnut-sized cauliflower-like, slightly pinkish moist tumour in the perianal region. After only two injections of Bleomycin (3 mg and 15 mg) intravenously there was almost complete regression of the tumour (Fig. 8). Complete disappearance of the lesion occurred (Fig. 9) 3 weeks after inception of therapy, with a total of 93 mg Bleomycin. Bleomycin was continued until a total dose of 123 mg was reached. There has been no recurrence of the lesion during a 3 month follow-up period. Similar excellent response has been observed in the treatment of multiple verrucae vulgares of a 20-year-old male and 13-year-old female who wished non-electrosurgical treatment because of cheloid constitution. The lesions disappeared following one or two systemic injections of Bleomycin as shown in the representative Figs. 10 and 11.

The toxic side effects of Bleomycin administration have been described in detail elsewhere (4, 6, 7). In spite of the absence of hematologic changes, continuous systemic administration of Bleomycin may sometimes cause pneumonia-like symptoms, the only serious known side effect of Bleomycin. This was also observed in one of our cases of prickle cell carcinoma. It has been recommended to pay special attention to pulmonary changes and symptoms in the course of systemic Bleomycin treatment, particularly beyond the total doses of 200 mg. In addition, sclerotic change in fingers, cutaneous and nail hyperpigmentation, hair loss, anorexia, stomatitis, and fever occurring several hours after the injection have been noted in almost every case of continuous systemic administration. However, the withdrawal of the drug resulted in natural recovery.

CONCLUSION

Bleomycin has been used systemically in therapy of prickle cell carcinoma, reticulum cell sarcoma, verruca vulgaris and condyloma accuminatum with moderate to excellent clinical results. Although systemic administration is reported to be ineffective for the treatment of basal cell

epithelioma, this lesion can be effectively treated by local injections.

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Y. Mishima, M.D.
Department of Dermatology
Wakayama Medical University
1 Banchi, 7 Bancho
Wakayama-shi 640
Japan