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A preliminary study of the local treatment of preneoplastic and malignant skin lesions using methyl jasmonate

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Abstract. – *Background:* **Jasmonates are plant stress hormones. These small hydrophobic compounds exhibit anti-cancer activities, *in vitro* and *in vivo*, against cancer cells of various histological origins. Moreover, they show a selective activity against transformed cells and affect drug-resistant cells as well.**

Aim: **The aim of this study was to evaluate the activity of a powerful jasmonate derivative, that is methyl jasmonate.**

Material and Methods: **Methyl jasmonate was applied topically on cancerous and pre-cancerous skin lesions from eight patients.**

Results: **Methyl jasmonate did not cause any meaningful local or systemic side effects. Three patients exhibited positive responses. Two patients had complete recovery and one had a recurrence of the lesion three months post treatment.**

Conclusions: **Methyl jasmonate is a potentially promising novel topical treatment for prcancerous and cancerous skin lesions. Methyl jasmonate should be evaluated in a larger series of patients.**

Key Words:

Methyl jasmonate, Skin, Cancer, Topical treatment.

Introduction

The jasmonate family members, which consist of cis-jasmone (CJ), jasmonic acid (JA), and methyl jasmonate (MJ)[1], are fatty acid-derived cyclopentanones that occur ubiquitously in the plant kingdom.

These compounds are similar, in structure and biogenesis to prostaglandins, important signalling molecules in invertebrates and vertebrates[2,3].

Jasmonates act as signal transduction intermediates when plants are subject to environmental stresses, such as UV radiation, osmotic shock and heat.

In the past few years more than ten research groups have reported that jasmonates exhibit anticancer activity *in vitro* and *in vivo*. Jasmonates and some of their synthetic derivatives inhibit the proliferation and induce cell death in various human and murine cancer cell lines, including breast, prostate, melanoma, lymphoblastic leukemia and lymphoma cells[4]. Furthermore, survival studies showed that jasmonates increased the life span of T-cell lymphoma-bearing mice[4]. Jasmonates exhibit two desirable characteristics of anti-cancer drugs. First, they are highly selective towards cancer cells and ineffective towards normal cells. Indeed, MJ exhibited selective cytotoxicity towards cancer cells even when they were a part of a mixed population of leukemic and normal cells drawn from the blood of chronic lymphocytic leukemia (CLL) patients[4,5]. Second, jasmonates have the ability to act against drug resistant cells. This fact was demonstrated using a pair of B-lymphoma clones of the same line differing in their p53 expression, i.e. wild-type versus mutant p53. These clones differ drastically in their response to the cytotoxic drug Bleomycin and the radiomimetic neocarzinostatin (NCS), i.e. the mutant p53-expressing clone is by far less susceptible to these agents. In contrast, jasmonates were equally active against either clones[4,5].

As far as non-specific toxicity is concerned, non transformed lymphocytes and keratinocytes were unaffected by jasmonates, and intravenous administration of MJ to mice did not induce any toxicity[4-8]. Jasmonates were also discovered to have cytotoxic effects towards metastatic melanoma *in vitro* and *in vivo*[7,8].

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Three mechanisms have been proposed so far in order to explain their anti-cancer activities, including induction of severe ATP depletion in cancer cells via mitochondrial perturbation, induction of re-differentiation in human myeloid leukemia cells, via mitogen-activated protein kinase activity, and induction of reactive oxygen species-mediated apoptosis in lung carcinoma cells, via generation of hydrogen peroxide and proapoptotic proteins of the Bcl-2 family[10-12]. Recently, it has been reported that not only direct toxicity, but also MJ effects upon angiogenesis are relevant to its anti-neoplastic effects[13].

Jasmonates are also used as food additives, in cosmetics and they are sold commercially, but not as drugs.

Materials and Methods

We report the use of MJ, applied topically on some pre-malignant and malignant skin lesions. We performed an open trial on a compassionate basis, on eight patients and recorded their responses. Studies were performed according to the Helsinki and local International review board (IRB) rules (a formal waiver was granted), and the informed consent was gained. The patients were not surgical candidates because of the previous failure of a single or multiple surgery, the extent of cancer and clinical contraindications; they had been previously unsuccessfully treated with different drug schedules, including chemotherapy or local ointments. We used MJ in oil suspension at 1 g/ml. The compound was administered twice daily on the diseased skin or mucus for 4 weeks, covered by an obclusive poliurethan medication, in order to enhance the compound absorption. The patients were in the 56-73 age range. The pathologies included: oral lichen planus, sebaceous perineal cancer, lower leg ulcer with squamous cell cancer, lentigo maligna of the face with mixed basal spinal cells carcinoma, relapsed precancerous lesion of perineal skin, meningioma with temporomandibular joint and submucosal parapharingeal diffusion, squamous cell cancer of arm and lower leg and leukoplakia (Table I).

Results

MJ was well tolerated. No meaningful local or systemic side effects were detected. Specifically, no redness or itching of the surrounding skin or mucosa was observed after administration over the lesions.

Three out of the eight patients exhibited positive responses, i.e. the patient with oral lichen planus (Figure 1), and the patient with leukoplakia, had complete recovery (currently, for 18 months following the first treatment), while MJ treatment of the patient with lentigo maligna of the face resulted in dry tumor surface with reduction of the metaplastic area during treatment, but the cancer reappeared three months later.

Discussion

The development of squamous cell carcinoma is a feared complication of oral lichen planus. No therapy for oral lichen planus is curative, and prolonged topical administration of corticosteroids can produce side effects such as secondary candidiasis[14].

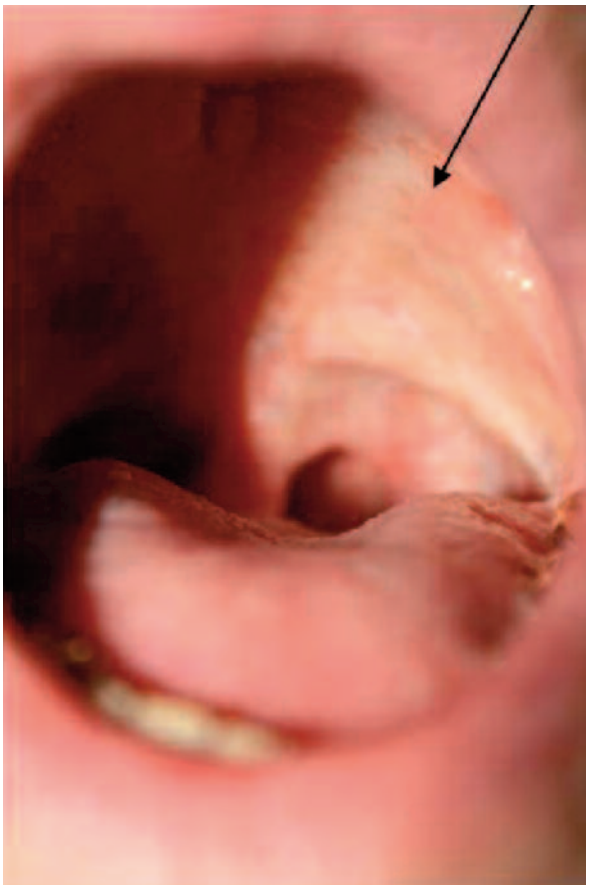

Figure 1. Oral lichen planus.

Table I. Treated cases.

Gender	Age	Pathology	Results
F	60	Oral lichen planus	Complete recovery
M	65	Sebaceous perineal cancer	No response
M	70	Squamous cell cancer from lower leg ulcers	No response
F	73	Lentigo maligna of the face with mixed basal spinal cells carcinoma	Positive response only during treatment
M	68	Relapsed precancerous lesion of perineal skin	No response
F	58	Meningioma with temporomandibular joint and submucosal parapharingeal diffusion	No response
F	56	Squamous cell cancer of arm and lower leg	No response
F	57	Leukoplakia	Complete recovery

When skin tumors malignancy manifested, local administration of MJ did not give us eradicating results, while oral lichen planus, lentigo and leucoplakia were very sensitive to treatment. This fact might prevent further surgical options, eventually limiting the eradication to minor invasive procedures like CO_2 and Herbium-YAG lasers.

It appears that a new treatment option for oral lichen planus is highly desirable. Our trial of MJ, applied topically to various skin lesions, resulted in 3 out of 8 positive responses. Interestingly, MJ was shown to induce a G_2/M phase cell-cycle arrest and non-apoptotic cell death in the human urogenital tract parasite *Trichomonas vaginalis*[15,16], further pointing towards possible topical uses of jasmonates.

The main mechanism of action of jasmonates is to dissociate hexokinase from the outer membrane of the mitochondria. It results in decreased glycolysis and mitochondrial permeability transition, leading to apoptosis[11,12]. Therefore, MJ could provoke bioenergetic catastrophe and eventually cell death in cancerous and pre-cancerous skin cells.

Further clinical trials, involving the use of MJ, are necessary in a larger series of patients with cancerous and pre-cancerous skin conditions.

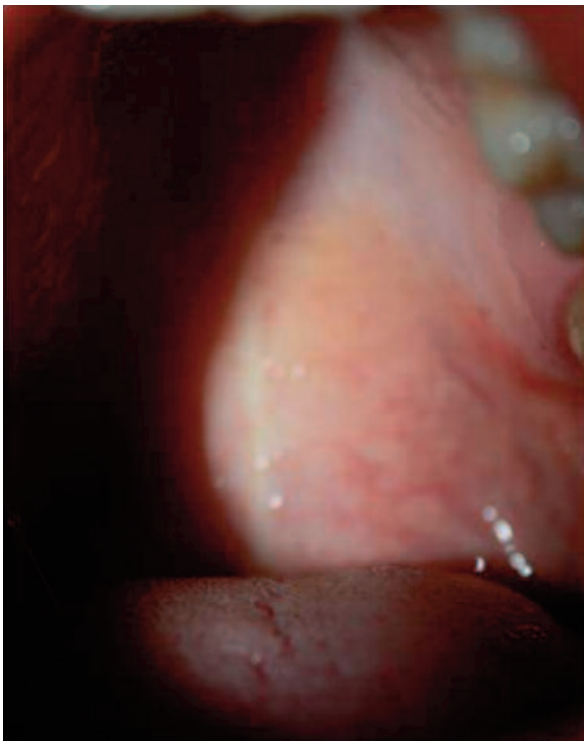

Figure 2. Lichen planus of the cheek mucosa.

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