原　著

THERAPEUTIC EFFECT OF ARSENIC TRIOXIDE CONTAINING LOTION IN A HUMAN BLADDER CARCINOMA XENOGRAFT MODEL

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ABSTRACT

BACKGROUND: Patients with metastatic carcinoma develop cutaneous metastases in about 10% of cases. These skin metastatic lesions are usually treated by radiation therapy and/or chemotherapy with disappointing results. In this study we used human bladder carcinoma xenograft nuice as a model to investigate whether arsenic trioxide lotion has an anti-tumor effect on skin metastases of human solid tumor cells. MATERIALS AND METHODS: Female BALB/c-Hfbllnu mice received subcutaneous injection to the left flanks on day 0 with 2 x 10^6 viable HTB-9 tumor cells. When the mean tumor size reached 7-8 mm at the 19th day, the mice were randomly divided into three groups of six mice. The first group was treated with the lotion containing no arsenic trioxide and served as the control group. The second group were given artificial wounds on tumors which were then treated with arsenic trioxide lotion. The third group was treated with the arsenic trioxide lotion on tumors. The treatment schedule was three times a week. The total dose of each treatment was 0.14 gm lotion (containing 0.0462 mg arsenic trioxide), which was applied to the skin over each visible tumor. RESULTS: There was a significant difference (P<0.05) in tumor growth between group 1 and group 2, and between group 1 and group 3 beginning from the 35th day after treatment, but there was no significant difference between group 2 and group 3. Arsenic trioxide lotion treatment delayed the growth of the

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Received for publication: July 29, 2004

subcutaneous bladder carcinoma regardless of whether the tumor was covered by skin or artificially wounded. CONCLUSION: The results of this study suggest that arsenic trioxide lotion is a worthy candidate for clinical trials.

Key words: Arsenic trioxide (ATO) Cutaneous metastasis Solid tumor

INTRODUCTION

Arsenic trioxide (ATO), a novel agent for treatment of newly diagnosed and relapsed acute promyelocytic leukermia (APML) without cross-resi stance to all-trans retinoic acid, has shown a unique and high response rate (80-90%)[1]. The effect of ATO may result in the induction of apoptosis, the inhibition of growth and anglogenesis, and the promotion of differentiation. Such actions have been observed in cultured cell lines and animal models, as well as clinical studies. Because ATO affects so many cellular and physiological pathways, a wide variety of malignancies, including both hematologic cancer and solid tumors derived from several tissue types, may be susceptible to therapy with ATO. The National Cancer Institute U.S. is working cooperatively with research centers across the U.S. to evaluate the clinical activity of ATO in hematologic malignancies, and is also supporting research of the effects of ATO in solid tumors, such as hormone-refractory prostate cancer, renal cell cancer, cervical cancer, and refractory transitional cell carcinoma of the bladder[3]. Cutaneous metastasis is not an uncommon manifestation but may develop from many malignancies, including breast, head and neck, lung, gastric, colorectal, hepatic, renal, cervical and ovary, bladder and prostate cancer[4]. Moreover, the unpleasant smell of infected fungating cutaneous metastatic tumor or malignant cutaneous ulcer is a distressing clinical problem. Arsenic containing treatment has a history of over two millenniums in western countries. Arsenic containing compounds have also been used to treat human disease for centuries in traditional Chinese medicine, with external use for superficial tumors such as cancer of cervix, skin, lips, penis, breast, as well as for intractable tinea infection, hemorrhoids and ulcers with local or focal necrosis. The purpose of this study was to evaluate the effectiveness of ATO as external lotion to treat the skin metastasis in a human bladder carcinoma xenograft murine model. The result of this study demonstrated a pronounced response to delay tumor growth after the topical external use of ATO containing lotion.

MATERIALS AND METHODS

Chemicals

The arsenic trioxide lotion is manufactured by TTY Blopharm Co., Ltd., Taiwan. It is an oil-in-water emulsion for topical administration for use in the treatment of subcutaneous tumors. The lotion is a white fluid, which contains 0.33 mg/g of arsenic trioxide and the following inactive ingredients: steanic acid, cetyl alcohol, anhydrous lanolin, vegetable oil, glycerin, and troethanolamine.

Animals

Female BALB/c-Hfhllnu mice (6 - 8 weeks old) were purchased from the National Laboratory of Animal Breeding and Research Center (Taipei, Taiwan). The animals were housed in sterile filter-top cages on sterile bedding, and maintained on an irradiated diet and autoclaved water.