Combined effect of topical arsenic trioxide and radiation therapy on skin-infiltrating lesions of breast cancer—a pilot study

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It has been reported that arsenic trioxide (As_2O_3) is an apoptosis inducer and radiation sensitizer for various cancer cell lines. In this study of breast cancer patients, we examined the combined effect of topical As_2O_3 and radiation therapy on fungating and/or skin-infiltrating lesions of breast cancer. The dermatological, gastrointestinal, hematological, renal and hepatic toxicities of the treatment were also monitored. As_2O_3 gel (0.05%) was applied to tumor lesions 1 h prior to delivery of each fraction, with the gel removed about 5 min before the irradiation. Superficial radiation was delivered using an electron beam from a linear accelerator. Every week, the tumor lesions were photographed to evaluate effectiveness, and blood was sampled to monitor changes in hemogram and biochemical profile. Seven breast cancer patients with cutaneous metastasis were enrolled in this study. In terms of tumor, the rates for complete, partial response and stable disease were 42.9 (three of seven), 42.9 (three of seven) and 14.3% (one of seven), respectively. The skin pain, assessed by a visual analog scale, and secretion from all of the seven superficial and fungating wounds decreased markedly after treatment. Significant bone marrow suppression or granulocytosis was not noted. Further, changes in renal and hepatic function were also not significant. It seems reasonable to conclude that As_2O_3 may be an effective and safe radiosensitizer for palliative radiotherapy for skin-infiltrating lesions of breast cancer. *Anti-Cancer Drugs* 14:825–828 © 2003 Lippincott Williams & Wilkins.

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Introduction

Early in the 20th century, arsenic compounds were used to treat chronic myelogenous leukemia and malignant lymphoma. Recently, arsenic trioxide (As_2O_3) has been used in the treatment of *de novo* and refractory acute promyelocytic leukemia (APL) patients, with high rates of response and hematological/molecular remission achieved [1]. Clinical response has also been obtained for patients with human T cell lymphotropic virus type I-associated adult T cell leukemia/lymphoma [2]. Further, As_2O_3 inhibits cell growth and induces apoptosis in certain types of cancer, including APL [3], hepatoma [4] as well as pancreatic [5] and gastric [6] carcinomas.

Chun *et al.* have demonstrated that As_2O_3 can sensitize human cervical cancer cells to ionizing radiation, both *in vitro* and *in vivo* [7]. In combination with ionizing radiation, As_2O_3 pre-treatment has a synergistic effect with respect to decreased clonogenic survival and regression of established human cervical tumor xenografts [7]. At the time of writing, however, the combined effect of As_2O_3 and radiation on clinical cancer patients had not been reported.

In our preliminary investigation of cutaneous metastatic breast cancer, it was demonstrated that topical As_2O_3 improved local tumor control and decreased wound secretion without significant systemic or local adverse effects [8]. In the present study, we examined the efficacy and safety of radiation in combination with As_2O_3 pre-treatment for palliation of superficial malignant lesions in breast cancer patients. For efficacy assessment, the diameters of involved skin metastasis area, pain score and daily needed frequency of changing the dressing (CD) were recorded. The dermatological, gastrointestinal, hematological, renal and hepatic toxicities of the treatment were also monitored for safety consideration.

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Patients and methods

Patients and clinical protocol

Between December 2001 and March 2003, seven breast cancer patients with superficial fungating or skin-infiltrating tumors who had undergone standard treatments received topical As_2O_3 and radiotherapy at Mackay Memorial Hospital (Table 1). Eligibility criteria for the study included diagnosis of breast cancer confirmed by pathological examination. In addition, patients had to have relapsed after standard treatments such as surgery, radiation therapy or chemotherapy. Six patients had received post-operative radiation to the chest wall and axillary area. Written informed consent was required, and the study protocol was reviewed and approved by the institutional review board of the Mackay Memorial Hospital.

Treatment program

As_2O_3 gel (0.05%; TTY Biopharm, Taipei, Taiwan) was administered in daily topical doses that ranged from 0.05 to 0.15 mg/cm^2/day (usually 0.1 mg/cm^2/day). The gel was administered 1 h prior to the daily radiation treatment and was subsequently removed 5 min prior to the radiation exposure. Electron beam radiotherapy was delivered using a linear accelerator (9–12 MeV, dose rate 2.4 Gy/min; Clinac 1800; Varian Associates, Palo Alto, CA). Radiation was administered 5 days a week (total dose: 50 Gy in 25 fractions or 30 Gy in 10 fractions). To avoid skin-sparing at high electron energy, 0.5–1.0 cm tissue equivalent bolus was used before radiation.

Assessment of response

Observation for tumor response and skin reaction was conducted daily, with photographs taken weekly. A complete response was defined as the disappearance of all known skin lesions within radiation fields confirmed by subsequent observation at least 4 weeks apart. A partial response was defined as a decrease in the sum of the maximal perpendicular diameters for the involved skin area within radiation fields by more than 50% which was confirmed by subsequent observation at least 4 weeks apart. Progressive disease was defined as at least 25% increase in the sum of the maximal perpendicular diameters for the involved skin area or the appearance of new lesions within radiation fields. All other tumor outcomes were classified as stable disease. For efficacy of pain control, chest wall pain was estimated using a visual analog scale (VAS) as a subjective assessment. The VAS scores before treatment were set as the baseline for every patient, and we compared the changes between subsequent data after treatment and the baseline data. When differences were greater than 50 mm in a 100-mm scale, we identified this patient as a responder. The daily need for changing dressings (CD) of wounds was also recorded by nurses in charge of each patient.

Monitoring for adverse effects

With regard to drug absorption via skin, possible systemic adverse effects were evaluated. Serial blood counts and serum chemistry profiles were performed. Serum chemistry profiles, including alanine aminotransferase, aspartate aminotransferase, blood urine nitrogen and creatinine, were measured using a Synchron LX20 spectrophotometer (Beckman Coulter, San Diego, CA). An electrocardiogram was recorded before and after irradiation for each patient. Adverse effect and toxicity were evaluated according to the Common Toxicity Criteria (CTC) version 2.0 published by the DCTD, NCI, NIH and DHHS in 1999.

Results

Treatment efficacy

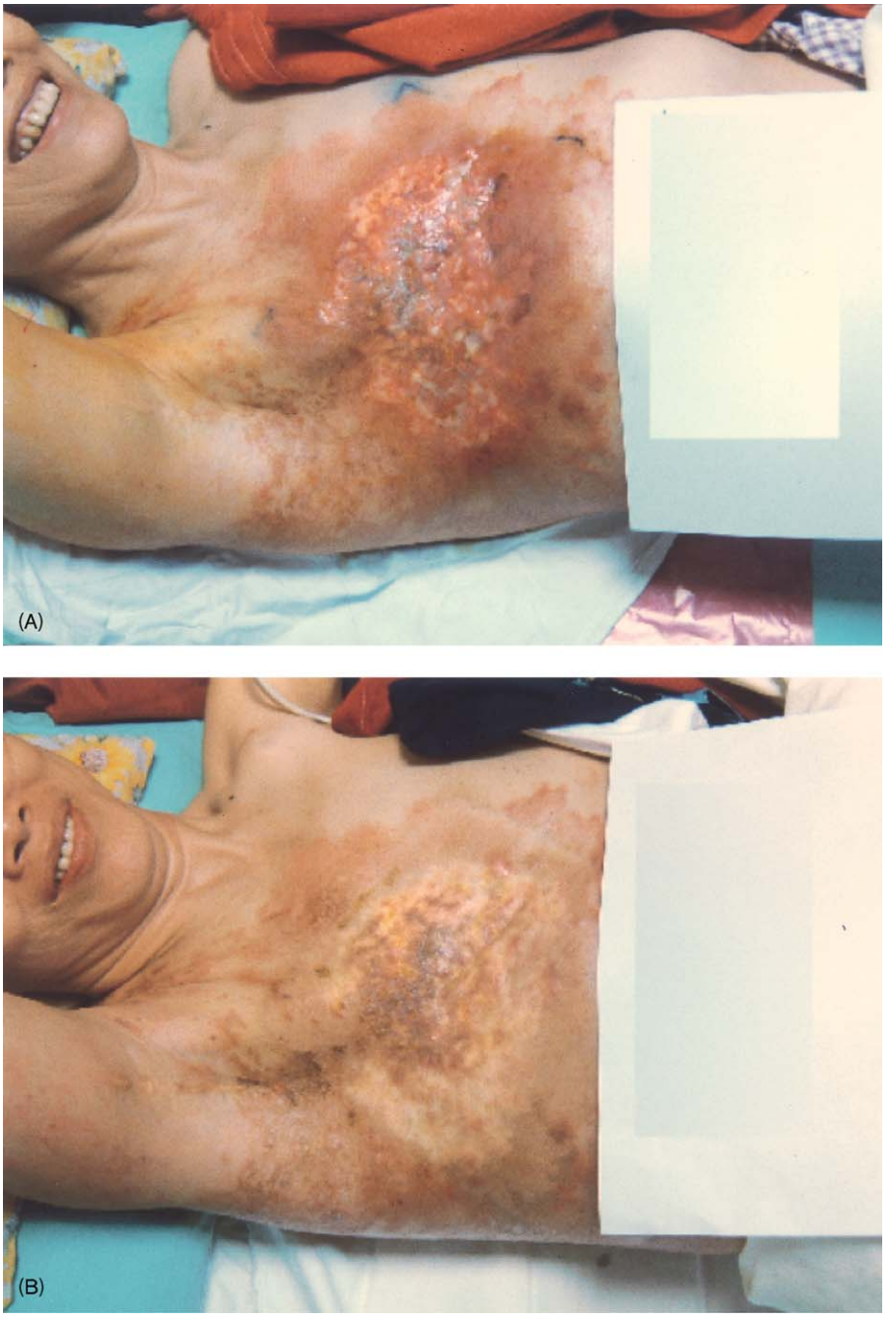
Complete remission was achieved for three patients with chest wall skin-infiltrating lesions with one demonstration in Figure 1. The cumulative radiation dosages for remission of these chest wall skin lesions were 20, 22 and 28 Gy, respectively. Partial remission was achieved for another three cases with chest wall fungating tumors (Table 2). One patient with chest wall fungating tumor proved resistant to this combined therapy and was classified as a stable disease. The radiation dose for each patient is listed in Table 2. The wound secretion from all of the superficial and fungating wounds was markedly decreased with a change in mean daily needed CD frequency from 4.4 to 0.9 after treatment for 1 month. Relief of chest wall pain assessed by the VAS was achieved for all of these seven patients (Table 2).

Table 1 **Patient characteristics**

Patient	Gender	Age	Cell type of primary malignancy	Type of lesion	Pre-radiotherapy WHO performance status
1	female	53	IDC	skin infiltration	1
2	female	46	IDC	skin infiltration	2
3	female	62	LIC	skin infiltration	2
4	female	33	IDC	fungating tumor	2
5	female	41	LIC	fungating tumor	2
6	female	57	IDC	fungating tumor	3
7	female	71	IDC	fungating tumor	3

IDC: infiltrating ductal carcinoma; LIC: lobular invasive carcinoma.

Fig. 1



Skin-infiltrating tumor of a breast cancer patient (patient 1): (A) before combined treatment and (B) 3 weeks after combined treatment.

Adverse effects

Table 3 shows the maximal adverse effects developed during and after this combined treatment. The most severe acute radiation dermatitis observed in the study was grade 3 in two patients; however, it had healed satisfactorily 2–3 weeks after completion of the radiation treatment, with none of the patients developing grade 3 chronic radiation dermatitis. No grade 2–4 granulocytosis or leukopenia was noted during the combined therapy. Other adverse reactions included light-headedness during irradiation and moderate fatigue after radiation; however, no changes in performance status were evident. Further, there were no skin pigmentation or significant changes in renal or hepatic function during the course of the combined treatment. Prolongation of the electrocardiogram Q–T interval was not noted.

Table 2 Response to treatment

Patient	Radiation dose (Gy)[a]	Tumor response	Change in daily need of wound CD	Reduction in VAS for skin pain (mm)
1	50	complete	6→0	75
2	50	complete	4→0	65
3	50	complete	4→0	80
4	50	partial	5→1	70
5	50	partial	3→1	65
6	30	partial	5→2	75
7	50	stable	4→2	55

[a]A dose of 50 Gy was delivered in 25 fractions; 30 Gy in 10 fractions.

Table 3 Adverse effect and toxicity

	CTC grade				
	0	1	2	3	4
Granulocytosis	6	1	0	0	0
Leukopenia	7	0	0	0	0
Thrombocytopenia	7	0	0	0	0
Nausea	4	2	1	0	–
Anorexia	4	2	1	0	0
Vomit	6	1	0	0	0
Acute radiation dermatitis	1	1	3	2	0
Chronic radiation dermatitis	4	2	1	0	0
Fatigue	3	2	2	0	0
Hyperpigmentation	7	0	0	–	–

The number shown below grade 0–4 is the case number who developed the adverse effect.

Discussion

In our preliminary investigation of topical As_2O_3 treatment for cutaneous metastatic breast cancer, no significant systemic absorption of As_2O_3 was determined from a pharmacokinetic study [8]. Additionally, besides the decreased wound secretion and improved local tumor control, other benefits including drying of the skin lesions and reduction in unpleasant odor were also noted.

About 10% of patients with metastatic carcinoma have cutaneous metastases. Management of these metastatic skin lesions with radiation therapy or chemotherapy is usually disappointing. In this study of superficial malignant lesions from breast cancer, we found that combining topical As_2O_3 and radiation therapy not only resulted in satisfactory tumor response, but also achieved a good palliation.

As_2O_3 can arrest the tumor cell cycle at the G_2/M phase [9], with tumor cells most sensitive to radiation at this stage of the cycle [10]. This may produce sensitization of the tumor cells to radiation [11].

A higher clinical response rate in this pilot study was achieved for the combination of topical As_2O_3 and radiation treatment (42.9% complete remission and 42.9% partial remission) in comparison to topical As_2O_3 alone [8]. In view of these favorable results, it seems reasonable to suggest that combining topical As_2O_3 and radiation may achieve better local control for superficial malignant lesions and further clinical study is recommended.

As As_2O_3 has both apoptosis- and differentiation-inducing activities, development of granulocytosis is a common feature of its clinical use for systemic treatment of leukemia [1]. In our study, however, no significant hematological changes were observed. A possible explanation for this finding is that removal of the gel prior to irradiation limited circulatory penetration.

Further, although dermatological toxicity such as skin rash has been demonstrated for topical As_2O_3 treatment [12], we did not note any toxicity of this type, perhaps due to the modest duration of daily application (less than 1 h) and treatment (not more than 5 weeks).

With respect to quality of life, the combination of As_2O_3 and radiation treatment appears to offer an effective, tolerable and safe treatment modality for palliative care of breast cancer patients suffering from superficial malignant lesions. Although the results of this pilot study are promising, the limitation of the small number of patients enrolled and no specific comparison to the efficacy of radiation alone make further randomized phase III trials necessary.

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