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ORIGINAL ARTICLE

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4,4′-Dihydroxybenzophenone-2,4-dinitrophenylhydrazone (A-007): a topical treatment for cutaneous metastases from malignant cancers

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Abstract *Purpose*: This study is to document the activity and acceptability for a new topical agent, A-007, in the treatment of cutaneous metastases from cancer. *Patients and methods*: This is a multicenter study involving 27 patients with inoperable skin lesions from histologically confirmed cancers of the breast and oral cavity, non-Hodgkin's lymphoma, Kaposi's sarcoma, and angiosarcoma that had failed radiotherapy or systemic treatment. A-007, as a 0.25% gel, was applied twice daily to the areas of cancer to be measured as well as applied to a healthy control area distant from the cancer areas. An untreated cancer area was also included and documented as a cancer control. *Results*: The overall objected response rate with A-007 was 26%, with an additional 19% minimum response/stabilization of cancer. For patients with breast cancer, hormonal status did not have an impact on response. The median duration of response was 15 weeks (with one patient having a response for 3.5 years). Toxicities observed were itching, burning, and a rash, in 6 of the 27 patients. The skin toxicities were in the cancer-treated fields; none were observed in the A-007 control areas. All irritated areas cleared while continuing treatment, and the tumor lesions in the areas of itching also improved. *Conclusion*: A-007, as a 0.25% gel, is confirmed as an effective palliative treatment option for cutaneous metastases from cancers. Skin reactions were minimal, tolerated, and no cessation of treatment was required.

Keywords 4,4′-Dihydroxybenzophenone-2,4-dinitrophenylhydrazone · Cutaneous metastases · Breast cancer · Melanoma · T-cell lymphoma

Abbreviations A-007: 4,4′-dihydroxybenzophenone-2,4-dinitrophenylhydrazone

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Introduction

The incidence of chest wall recurrences in patients with breast cancer is between 10 and 30% [1, 2]. In the majority of the cases (80–90%), the recurrences are multifocal at the time of presentation and 50% reflect distant metastases [1–3]. Melanoma and cutaneous T-cell lymphoma have high incidences of metastases to the skin (~ 30–75%) [4, 5]. Kaposi's sarcoma (KS) is a multifocal cutaneous disease that involves the skin as well as visceral organs [6]. KS cutaneous lesions were also included in the study.

Cancer usually spreads to the skin via the lymphatic network of the papillary and reticular dermis [3, 4]. Breast cancer metastatic to the skin is poorly vascularized and often resistant to systemic and local therapy, resulting in classical ulcerative lesions—*carcinoma encuirasse* [3]. Due to poor vascularization, chemotherapeutic agents often have reduced penetration of the

dermal tumor bed and are unable to kill cells directly. A therapeutic modality that could penetrate and effectively manage cutaneous/skin metastases could be an addition to systemic protocols.

4,4′-Dihydroxybenzophenone-2,4-dinitrophenylhydrazone (A-007)

4,4′-Dihydroxybenzophenone-2,4-dinitrophenylhydrazone (A-007) is a triaryl hydrazone that produced objective responses when applied topically (in dimethyl sulfoxide) to dimethyl benzanthracene (DMBA) induced rat mammary breast tumors growing in rat mammary glands [7]. Initially, A-007 was considered to be an antiestrogen because of its structural similarity to tamoxifen; however, the product did not bind with the estrogen receptor (G. Leclercq, Institut Jules Bordet, Brussels, personnel communication). During preclinical studies, A-007 was observed to upregulate both cutaneous and systemic T-lymphocytes, in particular CD4/8+ lymphocyte subtypes [8, 9]. The current mechanism of action for A-007's immune modulation properties is thought to be through the upregulation of the CD45 T-lymphocyte cell surface receptor. A-007 did not penetrate into the skin dermis (remained locally in the epidermis) was well tolerated when applied topically, upregulated naïve CD45RA CD3+ T-lymphocytes and was not absorbed into the systemic circulation [8–11]. No toxicities were noted in the preclinical animal studies, which would have precluded the product's use in humans [8, 10].

In the current study, the objectives were to assess the acceptability of A-007 topically applied to cutaneous cancer lesions through monitoring systemic and local toxicity, measuring objective responses and duration of response (DR) [12, 13].

Patients and methods

Patient eligibility

Participants enrolled were greater than 18 years of age. Inclusion into the study was restricted to those patients who had progressive cutaneous (intra- and/or subdermal lesions) and had failed surgery, radiation therapy, standard systemic endocrine therapy, and/or chemotherapy. Objective responses were documented on all patients by measuring and treating at least one lesion or groups of lesions and observing a second untreated lesion(s). In all patients a healthy skin area was also treated with the agent daily and reactions were monitored.

Primary basal and squamous cell cancers of the skin were excluded from entry into the study. Additional eligibility criteria included life expectancy of at least 3 months, at least 4 weeks lapse since prior chemotherapy or radiotherapy, adequate hematological function (absolute neutrophil count (ANC)$\geq 1.5\times10^9/mm^2$; platelet count $> 90\times10^9/mm^2$), adequate renal and hepatic functions (serum creatinine < 1.5 mg/l; bilirubin < 1.5 mg/l; ALT, AST and alkaline phosphatase < 2.5 times the upper limit of normal ranges). A Karnofsky performance status (PS) of ≥50 was required so that the patients could complete sufficient treatment and be evaluated. Exclusion criteria included progressive systemic metastases; a second primary malignancy within the last 5 years, except for treated and cured carcinoma in situ of the cervix, nonmelanoma skin cancer, or benign cutaneous lymphoepithelioma; major surgery; and/or concomitant treatment with other investigational drugs within 3 weeks prior to entering the study. Patients presenting with an uncontrolled, coexisting medical illnesses, not related to cancer—cardiac, pulmonary, endocrine, coagulopathies—severe enough to prevent completion of the study, lactation or pregnancy, or women of child-bearing potential not using adequate contraception during the last 3 months prior to entry into the trial or planned during the trial were excluded enrollment in the study.

Radiation therapy to cancerous sites outside of the treatment field was permitted during the A-007 therapy. Endocrine therapy was allowed to continue as long as the patient had been on therapy for at least 6 weeks before entering the study and no activity had been noted in the skin lesions that were being evaluated.

HPLC analysis of plasma A-007

The HPLC analysis for A-007 in plasma was performed according to the method of Rodgers et al. [14]. The assay had a limit of detection of 5 ng/ml of A-007 in plasma.

Treatment plan

This was a single-arm multicenter trial. Eligible patients were evaluated for the agent's acceptance, toxicity, and objective responses. The treatment end points—treatment until toxicity, progression of cancer, or complete response (CR)—were incorporated into parameters for both efficacy and acceptance.

A history and physical examination and complete blood count (CBC), chemistries including liver function, coagulation studies, EKG, and urine analysis were done prior to initiating the study. Weekly CBC, and complete chemistry profile were done weekly ×8 weeks then every second week. Local tumor responses were monitored weekly ×8 weeks then every second week and 2 weeks after the last treatment. Patients with CRs were followed-up until relapse.

Treatment

Drug: A-007, as a 0.25% propylene glycol gel, was made available as a clear, orange gel in plastic tubes, 22 g per

tube (prepared by Pharmaceutical Services, University of Iowa, Iowa City, IA, USA).

Dose and mode of application

A-007 failed to demonstrate local or systemic toxicity with an oral toxicity of >1,200 mg/kg [8, 10, 15]. The drug was well tolerated via topical administration (>1.5 g/kg) [8]. Corbett's "1,100 mg/kg total dose" rule defines that an agent having therapeutic activity >1,100 mg/kg should be considered for another route of administration [15]. This level of toxicity qualified the drug for an alternate route of administration—topical (T.H. Corbett, personnel communication).

Preclinical rat studies suggested that 3 mg/cm^2/week (median) of A-007, applied twice daily, produced 75% complete remissions in DMBA rat mammary breast tumors [7, 16].

Using FDA/Center for Drug Evaluation and Research (CDER) guidelines (http://www.fda.gov/cder/cancer) the initiating dose used in the study was ~2 mg/cm^2/week [8]. The total dose administered varied upon the size of area requiring treatment plus every patient had a different degree of skin induration (See below—Dose and mode of application and Results).

The gel was applied twice daily. Enough gel was applied to the measured areas with a gloved finger or a Q-tip cotton applicator, to cover the area that was to be treated and monitored. A nonocclusive medical dressing or gauze was applied to the area. A healthy control area, approximately 1×1 cm, was treated in all patients to document contact dermatitis or sensitivity to the A-007. All tubes were returned weekly and weighed to document the amount of agent dispensed.

Schedule modification

The standard dose and duration of treatment could be modified if local skin reactions occurred. The initial dosing could be reduced to once a day and then every other day. If necessary, treatment could be withheld for up to a week to allow improvement of symptoms. After symptoms improved and the patient wished to continue, the treatment could be reinitiated or the patient could be withdrawn from the study. New lesions that occurred outside of the originally treated area could be treated. The first five patients received a maximum of 22 g of gel (one tube) per week; enough gel to cover a measurable tumor site, as well as applied to a 1×1-cm noncancerous healthy skin (control) site—to monitor overall acceptability. After treating the first five patients no toxicities were observed with 22 g of gel per week, patients with larger lesions requiring more of the drug and could be treated with a sufficient amount of gel dispensed to cover all lesions.

Escalation

No dose escalation was involved.

Duration of treatment

Unless the patient developed intolerable local skin reactions, A-007 treatment was continued until progression of the local cancer occurred, toxicity developed or distant metastases worsened. If a CR occurred, the patient was asked to apply the A-007 gel to the treated areas for at least another 4 weeks.

End points

Response: Skin lesions were assessed (description, measurement) at base line and then were assessed weekly during each visit and 2 weeks after the last treatment. Patients who responded were followed until relapse. Photographs were taken at the baseline, if possible, and after the study—unless the patient refused.

Responses of lesions treated and overall response were calculated by measuring two diameters with a caliper, then by substituting values:

$$\text{Total tumor area (cm}^2) = \pi \times \frac{\text{length}}{2} \times \frac{\text{width}}{2}$$

Complete response was defined as the complete disappearance of all treated lesions for at least 4 weeks without the appearance of any new lesions within the treated area. Partial response (PR) was defined as a decrease by at least 50% of the sum of the products of two perpendicular diameters without the appearance of any new lesion within the treated area. No change (NC, stable disease) was defined as a decrease in size of less than 50% or an increase of less than 25%. Progressive disease (PD) was defined as an increase in size of 25% of any measurable lesions within the treated area (with reference to the smallest size of the lesion recorded during the study period in case of transient regression). All remissions had to be confirmed by a second observer.

Neither the occurrence of new skin lesions outside the treated areas nor the development of systemic disease was considered as evidence of PD or treatment failure. If new skin lesions developed outside the treated area, the field of treatment could be expanded. However, if systemic lesions progressed and systemic therapy was necessary, patients were withdrawn from the study.

Duration of response (DR) was defined as the time from the start of a response to failure. The following events were considered to be treatment failures: (1) progressive growth of any treated skin lesion according to the WHO definition; (2) development of any new lesions within an adequately treated area; (3) withdrawal of the patient because of poor tolerability of the study medication; and (4) withdrawal because of noncompliance, refusal or death of the patient.

Time to response (TR) was defined as the median time to a response (in weeks).

Safety and adverse drug events (ADE)

Blood samples were taken, prior to starting treatment and weekly during treatment, for complete blood and differential counts (CBC), complete chemistry profiles that included electrolytes, liver/renal function parameters, and plasma values for A-007 concentrations. Any untoward changes in the patients' conditions, excluding progression of cancer, were regarded as an adverse event, irrespective of whether the events were considered related to the study treatment. The time of onset, severity, and duration and causality of ADEs in relation to the study treatment were assessed.

Definition of dose-limiting toxicity (DLT)

Toxicity was graded according to the NCI cancer therapy evaluation program (CTEP) common toxicity criteria (CTC)—2.0 (http://ctep.info.nih.gov/reporting/ctc.html). Cutaneous adverse events were recorded in detail—Table 1. This cutaneous grading is an overview of individual symptoms and was modified from Leonard et al. [2]. The following symptoms were graded at each visit: subjective symptoms (including burning, itching, pain, and others) and objective symptoms (including erythema, skin dryness, desquamation, and others).

Quality control

This study was conducted under an investigational new drug application according to the FDA guidelines for good clinical practices (GCP). The study protocol, the patient consent forms, and all amendments relevant to the subjects' risks/benefit relationship were reviewed and approved by independent investigational review committees relevant to the centers involved.

Results

Twenty-seven patients [9 males and 18 females] ranging in age from 30–86 years (mean age 64) with cutaneous lesions were included in the study—breast cancer (12), melanoma (5), angiosarcoma (2), Kaposi's sarcoma (4), T-cell lymphoma (3), and head/neck cancer (1) (Table 2). Eleven patients completed 16 or more weeks on study. One patient (with T-cell lymphoma) was treated for 52 weeks and remained in remission for 3.5 years (Table 3). Patients who withdrew from the study prior to completing 16 weeks of treatment did so due to progression of their cutaneous/systemic diseases. No patients withdrew from the study because of adverse effects of A-007.

Table 1 Grading for cutaneous reaction [2]

0 = None or no change if symptom(s) initially present
1 = Mild reaction—only objective symptoms such as skin dryness, erythema, or desquamation
2 = Moderate—subjective symptoms—local pain, burning, or itching
3 = Significant—subjective and objective symptoms—macular, papular or vesicular eruptions
4 = Severe—exfoliative dermatitis or ulcerating dermatitis
5 = Not assessable

Response (Tables 2, 3, 4)

The overall objected response rate with A-007 was 26%, with an additional 19% minimum response/stabilization of cancer. For patients with breast cancer, hormonal status did not have an impact on response. The mean response period was 28.6 weeks (with one patient having a response for 3.5 years). One patient (#2) with extensive melanoma satellitosis demonstrated a response in a nontreated lesion distal to the treated field.

Tolerance and adverse effects (Tables 3, 4, 5)

Adverse events (ADEs) observed included A-007-associated skin itching, stinging, and burning of application sites (grade 2 skin reactions at tumor site) (Table 5). No toxicity was noted in the A-007 control (healthy) treated skin sites. The observed skin toxicities were not dose related—seen in patients receiving 0.1–6.3 mg/cm^2/week of A-007. All skin reactions cleared with continued use of A-007. No visceral or neurotoxicity was noted.

Of interest is that the ADEs occurred in those patients who were responding with shrinkage of their skin lesions.

Hematology, chemistry, and urine analysis (Table 5)

Complete blood counts, chemistries, and urine analyses were closely monitored throughout the study for all the patients. Abnormal blood counts and chemistries could be associated with patient deterioration from advancing cancer. One patient with Kaposi's sarcoma bled from small bowel intestinal lesions resulting in a grade 2 anemia requiring transfusions.

Histological profiles (Figs. 1, 2)

Metastatic cancer to cutaneous and dermal lymphatic channels presented as expanding nests of cancer cells that responded to topical A-007 with pyknosis and cancer cell death (Figs. 3, 4).

Table 2 Patient characteristics and responses

Characteristic(s)	Number of patients ($n = 27$)	Response(s)
Age (years)		
Mean	64	
Range	30–86	
Weight (kg)		
Mean	76	
Range	53–110	
Karnofsky performance status (PS)		
≥90	10	1 CR, 3 PR, and 5 stable
80	15	3 PR and 2 stable
70	1	0
60	1	0
Disease involvement		
Skin	27	1 CR, 7 PR, and 7 NC
Pulmonary[a]	3	0
Gastrointestinal[a]	3	0
CNS[a]	0	0
Bone[a]	4	0
Breast cancer	12	
Hormonal status		
Postmenopausal	12	1 CR, 1 PR, and 4 NC
ER/PgR		
+/+	4	1 PR, 2 NC, and 1 NR
+/−	2	2 NR
−/+	1	1 NR
−/−	5	1 CR, 2 NC, and 2 NR
Melanoma	5	2 PR and 3 NR
Angiosarcoma	2	1 PR and 1 NR
Kaposi's sarcoma	4	2 PR and 2 NR
Head/neck	1	1 NR
Non-Hodgkin's lymphoma	3	1 PR, 1 NC, and 1 NR

CR complete response, *PR* partial response, *NC* no change, *NR* no response, *ER* estrogen receptor, *PgR* progesterone receptor
[a]Untreated disease involvement

Amount of A-007 applied (Table 3)

Attempts were made to document the actual amount of A-007 gel used by each patient. Prior to dispensing each tube of gel, it was weighed in duplicate and numbered. Each week the patients returned their used tubes for new tubes. The used tubes were weighed in duplicate and the difference recorded. The average weekly dose of the pure drug ranged from 0.1 to 11.5 mg/cm^2. The first five patients received a maximum of 22 g of gel per week applied to selected cutaneous lesions. After five patients were treated and no toxicity noted (and responses seen), all measurable cutaneous lesions were treated.

Median TR (Tables 3, 4)

The length of A-007 therapy to produce a response varied from lesion to lesion, even in the same patient. Objective responses were first noted as early as 2 weeks and as late as 5 weeks after treatment was initiated (median—fourth week, range 2–5 weeks). Median DR was 15 weeks, (2–186 weeks)

Concurrent treatments

Tamoxifen and megestrol acetate were the only concurrent antineoplastic agents administered during the trials with A-007. The former two agents must have been initiated at least 6 weeks prior to A-007, and the A-007-treated cutaneous lesions must have failed to respond to the antihormone therapy.

Plasma levels for A-007

Plasma A-007 levels were measured weekly for all patients—during and after treatment using a reported verified GLP assay [14]. A-007 was not detected in any of the plasma samples (detection limits 5 ng/ml) from the 27 patients treated.

Discussion

A-007 is a triaryl hydrazone that was originally developed as an antiestrogen [8, 16]. Although, anticancer activity was noted in the DMBA breast tumor model, it possesses minimal to no antiestrogen activity in estrogen receptor-binding studies (G. Leclercq, Institut Jules Bordet, Brussels—personnel communication). A-007 has been thoroughly studied for toxicity when applied topically and systemically to animals [8, 10]. The product was well tolerated with no cytotoxic properties observed during comparative preclinical toxicology and pharmacology studies [8, 10].

The present study involved 27 patients treated topically with a 0.25% A-007 gel. Patients with melanoma, breast cancer, Kaposi's sarcoma and non-Hodgkin's lymphoma demonstrated objective responses [12, 13]. The objective response rate with topical A-007 in the current study is 26%. An additional 19% of the patients demonstrated minor responses and stable disease presentations, which in many cases were almost 50% objective responses. Responses occurred in the first 2–5 weeks of treatments with a median DR for 15 weeks (in one case for 3.5 years) [13]. For breast cancer, no associations were noted between tumor hormonal receptor values and responses to A-007.

Topicallly applied A-007 was not absorbed into the systemic circulation during the present human study. This agrees with the animal data [8, 10]. A-007 remains in the epithelial layer due to its highly electronegative structure and does not penetrate the basement membrane [8, 10]. In the Franz cell rat skin permeation studies, topical A-007 failed to demonstrate an ability to penetrate through the epidermis into the dermis and its subcutaneous vascular network [8].

Table 3 Tumor characteristics, amount of A-007 used and treatment responses

Patient #	Cancer/sites treated	Total dosage (mg)	Treatment duration (weeks)	Size of lesion(s) treated (cm) and responses	Average dose/week (mg/cm^2)	Type of lesions	Clinical response	Duration of response (DR) (weeks)
1	Breast/chest wall	290	17	16×27 → 7×13	1.7	Dermal cellulitis	PR	15
4	Breast/chest wall	170	16	3×3 → CR	1.3	Nodular-raised	CR	176
10	Breast/chest wall	238	16	27.5×7	0.1	Nodular-raised	NC	5
14	Breast/chest wall	97	3	16.5×14.3	0.2	Diffuse inflammatory	NR	
16	Breast/chest wall	52	2	3×3	3.3	Nodular inflammatory	NC	
17	Breast/scalp	501	17	5.2×3.5	5.9	Nodular cellulitis	NC	2
18	Breast/chest wall	270	17	3.5×3.3	1.8	Multinodular raised	NR	
19	Breast/chest wall	164	6	44×20.3	2.0	Maculopapules	NR	
21	Breast/elbow	24	2	2×0.7	6.0	Ulcerated nodular	NR	
24	Breast/neck	436	16	3.5×3.1	4.5	Weeping ulcers	NR	
25	Breast/chest wall	79	6	8.5×9	0.2	Inflammatory nodules	NR	
26	Breast/chest wall	185	4	42×38	0.1	Diffuse—*en cuirasse*	NC	
27	T-cell lymphoma	126	4	21.1×18.3	0.6	Maculopapules	NR	
29	T-cell lymphoma	1,919	52	3×2.5 → 0.3×0.25	6.4	Maculoerythematous	PR	186
30	T-cell lymphoma	2,296	16	8.25×10.3 → 7.5×9	2.1	Nodular erythematous	NC	16
2	Melanoma/leg	115	9	11×11 → 4.2×3	0.5	Satellite-nodules	PR	6
15	Melanoma/scalp	71	6	2.5×2.3	3.0	Nodular raised	NR	
20	Melanoma/leg	521	20	58.5×44 → 20.5×10	0.1	Satellites	PR	17
22	Melanoma/leg	109	5	5.8×5.2	4.6	Satellites	NR	
23	Melanoma/abdominal wall	16	4	5×5	0.1	Diffuse nodules	NR	
5	Angiosarcoma/scalp	77	3	6.5×5 → 2×1	1.5	Nodular-raised	PR	7
6	Angiosarcoma/scalp	39	3	14×10.5	0.3	Diffuse erythema	NR	
8	Kaposi's sarcoma arm	218	17	5×3.6 → 2×1.5	0.9	Diffuse erythema	PR	15
11	Kaposi's sarcoma/face	48	10	1.5×1.5	0.2	Nodular	NR	
13	Kaposi's sarcoma/leg	120	2	4.9×3	11.5	Nodular-raised	NR	
28	Kaposi's sarcoma/leg	20	16	1×0.5 → ~ 0.2	1.3	Dermal discoloration	PR	14
7	Head & neck	91	4	6×7	1.3	Indurated/weeping	NR	

CR complete response; *PR* partial response; *NC* no change; *NR* no response

Table 4 Response initiation/duration of therapy

Response to A-007 treatment ($N = 27$)	Parameter(s) measured (mean)
Average treated area	59 cm^2
Average dose (A-007)/week	2 mg/cm^2
Average weeks on treatment	13 weeks
Maximum weeks on treatment	52 weeks
Time to response (TR)	fourth week (median, 2–5 weeks)
Maximum response	182 weeks
Duration of response (Median)	15 weeks (median, 2–186 weeks)

The molecule is composed of at least three moieties—a nitrophenylhydrazone, a diphenylmethene, and a highly conjugated aromatic backbone. A-007 is very electronegative, due to its high degree of resonance and electronegative moieties, but not a reactive molecule [11, 17]. In preclinical studies, A-007 was excreted unchanged through the urine when administered orally [10].

A current mechanism of action for A-007 is that it penetrates into the epidermis, attracts and upregulates CD45+ T-lymphocyte [leukocyte common antigen (LCA)] subsets—predominately CD4+ and CD8+ cytotoxic lymphocytes [15]. The latter observations have been noted in guinea pigs, and rabbits treated with topical A-007 [15]. In the present topical study, acute contact dermatitis (ACD)—characterized by eosinophils grouped about superficial venules in association with edema, epidermotropic lymphocytes and Langerhan cell infiltrates—was not observed [12, 13]. The cutaneous areas biopsied did posses increased infiltrations of

Table 5 Toxicity: CTEP–CTC scale

Toxicity	CTEP–CTC scale			
	A-007 ($n = 27$)			
	1–2		3–4	
	No.	Percentage	No.	Percentage
Anemia	2	3.7	0	–
Itching	4	15	0	–
Itching and burning	1	4	0	–
Itching and rash	1	4	0	–

CTEP cancer therapy evaluation program, *CTC* common toxicity criteria—version 2.0

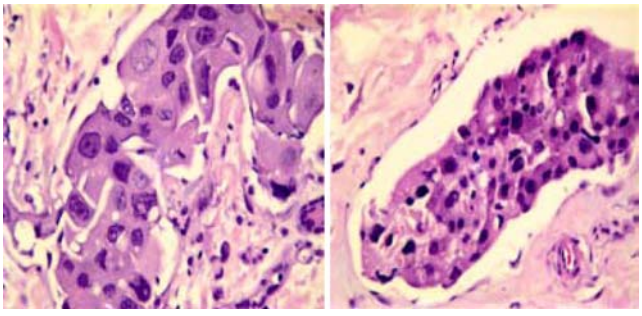

Fig. 1 Histology of metastatic breast cancer to the skin before (*left*) and after (*right*) topical A-007 therapy (daily over 2 months). Notice the shrinkage and pyknotic changes in the nucleus of the treated cancer cells on the right versus the pretreated (*left*). The patient was treated for 1.5 years with complete clearing of the area (*see below*)

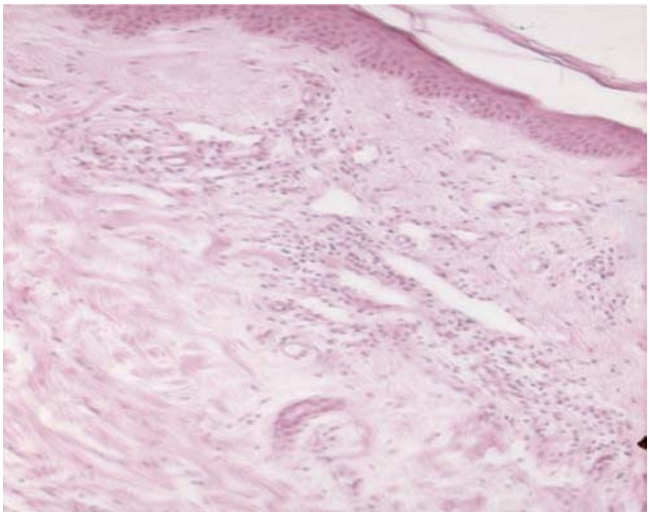

Fig. 2 Complete clearing of the above disease process with topical A-007 (1.5 years)

CD3+ T-lymphocytes in the dermis and epidermis in agreement with the animal and in vitro studies (Figs. 1, 2) [8].

In vitro studies by Easmon et al. [18] suggested that A-007 has alternate mechanism(s) of action via inhibition of thioredoxin reductase and blocking [14] C [cytidine] uptake [18]. The data generated in the study support A-007's ability to penetrate cutaneous structures that contain infiltrates of malignant cells. A-007's ability to modulate and upregulate lymphocytes is an interesting observation that needs to be further explored [9].

The primary end points of the study were progression of the treated areas, toxicity, progression of distant metastases, or a CR of a treated area. In the current study, no patient was withdrawn from the study because of toxicity; they obtained a complete response, had progression of local disease, or had progressive distant disease.

Systemically administered anticancer drugs have limited penetration into cutaneous lymphatic channels in which cancer cells have invaded. This is due to poor communication between the small arterial capillaries that deliver large/bulky chemotherapeutic agents and the capillary/malignant neovascular networks of cutaneous metastatic cancer lesions [3], [4], [6]. The electrostatic field effects of extracellular ground substance in skin can also be a natural barrier to drug–cancer cell surface interactions and penetrations [3].

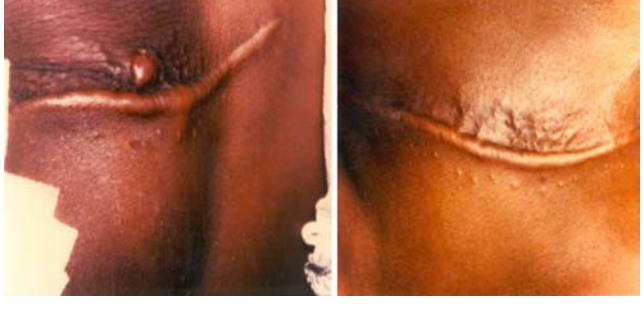

Fig. 3 Breast cancer recurrence—before (*left*) and after (*right*) topical A-007 (3.5 months)

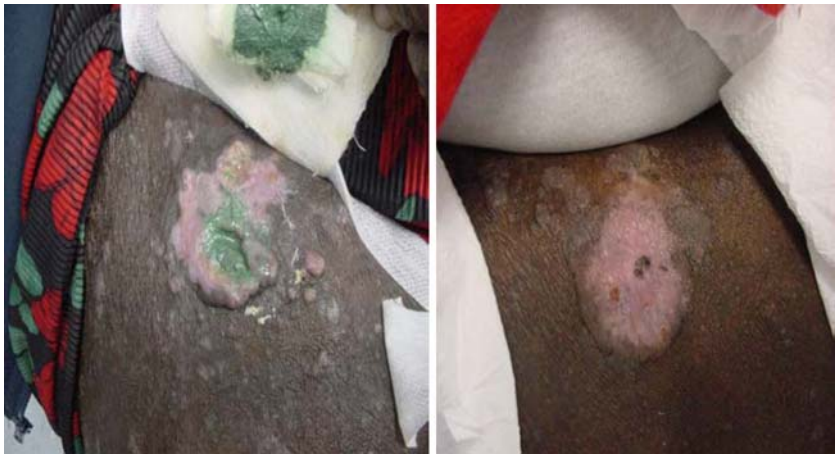

Fig. 4 T-cell lymphoma—before and during A-007 therapy (2.5 months)

Skin metastases from cancer can present a major psychological and cosmetic burden to patients [1–3]. In the absence of systemic toxicities, A-007 has promise to be incorporated into protocols with systemic therapy so that patients who are having a systemic response will not be discontinued from therapy because of resistant cutaneous metastases.

In summary, A-007 as a single agent produced objective responses and provided benefits for some of the patients treated. The most frequent skin reactions observed in the study were subjective symptoms—burning, itching, and—an objective symptom—a rash. One patient with Kaposi's sarcoma did bleed from intestinal lesions resulting in a grade 2 anemia. However, this was the only hematological toxicity noted. Overall, A-007 had a 100% global acceptance by the patients treated.

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