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ORIGINAL ARTICLE

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Miltefosine as a topical treatment for cutaneous metastases in breast carcinoma

Abstract *Background*: Recurrent cutaneous breast cancer is difficult to manage, with surgery, radiotherapy and systemic therapy all having their limitations. Miltefosine is a topical cytostatic agent which may provide an alternative approach in its treatment. *Patients and methods*: Patients with previously treated progressive cutaneous lesions from breast cancer were treated with miltefosine on a named-patient compassionate supply basis. Miltefosine was applied topically to the skin at a dose of 2 drops/10 cm^2 skin area. *Results*: Twenty-five patients were treated, most of whom had been heavily pre-treated. Treatment was continued for a median of 14 weeks (range 2–164). In 7 patients grade I skin toxicities were observed, and in 4 patients grade 3 local toxicities necessitated dose adjustments. A response was seen in 9 patients (1 complete response, 2 partial responses, 6 minor responses) giving a total response rate of 36%, with stable disease in 11 patients (44%) and progressive disease in 5 (20%). Those lesions which were superficial or <2 cm in diameter were most likely to respond. *Conclusions*: Miltefosine, either used alone or in conjunction with other therapies for distant metastases, is an effective and tolerable local treatment for cutaneous breast cancer.

Key words Cutaneous breast cancer · Cytostatic · Miltefosine · Topical therapy

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Introduction

Cutaneous local recurrences and skin metastases from breast cancer present a difficult clinical problem. They are frequently multifocal and often arise in areas which have previously been subject to surgical manipulation or intensive radiotherapy. For the patient, they are a daily visible reminder of the active status of their disease and can be a source of considerable anxiety and distress. The first treatment choice is usually surgical excision and/or local radiotherapy (including electron therapy), especially in the absence of distant metastases. However, surgical excision is usually only suitable for those lesions which are single, small and well vascularised, and radiotherapy options are often limited by previous chest wall irradiation. Systemic hormonal or chemotherapy is usually considered when surgery or radiotherapy are unsuitable or when skin lesions arise in the presence of distant metastases. However, diminished penetration of these agents as a result of vascular damage from previous surgery or radiotherapy often limits their efficacy.

Miltefosine solution (6% miltefosine solution: Miltex, ASTA Medica AG, Frankfurt, FRG) is a topically applicable cytostatic which has shown activity against cutaneous metastases from breast cancer and cutaneous T-cell lymphomas in early clinical studies [1, 2]. The active ingredient of miltefosine, hexadecylphosphocholine, is similar to naturally occurring phospholipids, allowing its incorporation into cell membranes where its main action is to inhibit membrane-linked protein kinase C and to interfere with membrane signal transduction [3].

Patients and methods

Over a period of 2.5 years, patients with progressive skin metastases from breast cancer for whom surgery or radiotherapy were not appropriate and who were either ineligible for an ongoing phase III trial of Miltex 2% versus 6% solutions or had progressed on the 2% arm of this trial were included. There were no restrictions

to concomitant treatments which were sometimes introduced to control distant metastases.

Miltefosine was supplied on a named-patient compassionate supply basis for use by the patients at home at a dose of 2 drops/10 cm^2 skin area, including a margin of 3 cm outside visible skin lesions. Miltefosine was applied directly to the skin with a gloved hand once daily for 1st week, and in the absence of toxicity, twice daily thereafter.

Results and discussion

The characteristics of the 25 treated patients are listed in Table 1. The median number of weeks of treatment was 14 (range 2–164) with 4 patients treated for 6–12 months and 4 patients treated for more than 12 months. In 5 patients, treatment was still ongoing at the time of data analysis. Ten patients had no concomitant systemic treatment at any time during miltefosine treatment, and 15 had systemic therapy at some point during miltefosine treatment (7 hormones, 7 chemotherapy, 1 hormones and chemotherapy) with no additional toxicity of either agent.

No systemic toxicity was seen with miltefosine, but grade 1 local toxicity occurred in a total of 11 patients: dryness (7), erythema (3), itch (3), broken skin/ulceration (3). In 4 patients, CTC grade 3 local toxicity occurred, requiring a 2-week treatment break for 2 patients and dose reduction to once daily application for 2 patients, in all instances with resolution of toxicities.

The best response to treatment was a complete responses in 1 patient, which lasted 18 weeks. Partial response was seen in 2 (8%) and minor response in 6 (24%), with respective median durations of response of 137 (range 114–160) and 6 (range 4–23) weeks, giving an overall response rate of 36%. Eleven patients (44%) had stable disease lasting a median of 18 weeks (range 4–104), and 5 patients had progressive disease. Five of 9 responding patients (56%), 9/11 (82%) with stable disease and 1/5 (20%) with progressive disease received concomitant systemic therapy at some point during miltefosine treatment.

The majority of patients had no difficulty with application and several patients clearly derived psychological benefit from their own participation in the treatment. The overall response of 36% is similar to the 23.4% described in a summary analysis of five phase II studies [4], giving useful palliation in this group of patients. Lesions most likely to respond to miltefosine were superficial lesions of <2 cm diameter or with lymphangetic infiltration [4].

Based on our experience, we would suggest that miltefosine is an effective and tolerable local treatment which offers the opportunity of self-treatment at home, and palliation of skin metastases which are unsuitable or refractory to other treatment modalities. It could be especially useful in frailer patients for whom systemic therapies are unsuitable and in delaying systemic therapies in those patients who have not yet manifested symptomatic distant metastases.

Table 1 Patient characteristics ($n = 25$)

	n	%
Age (years)		
Median (range)	54 (28–81)	
Sex		
Male	1	4
Female	24	96
Stage at primary diagnosis		
T1	5	20
T2	8	32
T3	1	4
T4	9	36
Tx	2	8
Prior treatment		
Surgery for cutaneous lesions	2	8
Radiotherapy		
Adjuvant to chest wall	15	60
Palliative to cutaneous lesions	13	52
No prior adjuvant radiotherpay	9	36
Prior adjuvant radiotherapy	4	16
Endocrine therapy	24	96
Number of previous regimes:		
1	8	32
2	7	28
3	7	28
4	2	8
Chemotherapy	19	76
Number of previous regimes:		
1	7	28
2	0	0
3	5	20
4	3	12
5	3	12
6	1	4

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