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Clinical report

Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast cancer patients

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Topical treatment of skin metastases with a cytotoxic agent is attractive for its easy self-administration and absence of major systemic interference. Miltefosine exerts its cytotoxicity by acting on cell membrane phospholipids and can be administered topically. Twenty breast cancer patients with progression of skin metastases were treated with a 6% solution of miltefosine, which was topically administered once daily during the first week and twice daily thereafter. Sixteen out of 20 patients also had metastatic disease at other sites. Concomitant systemic treatment when ongoing for at least 2 months prior to study entry was permitted, and consisted of chemotherapy and hormonal therapy in seven and nine patients, respectively. Prior palliative cytotoxic and hormonal therapy had been administered to 11 and 19 patients, respectively. No grade 3 and 4 toxicity occurred. Miltefosine therapy was discontinued in two patients due to nausea and in one patient due to skin toxicity. Grade 1 and 2 adverse skin reactions, and nausea and vomiting were seen in 11 and two patients, respectively. In 18 patients evaluable for response, four partial responses were noted (response rate 22%), while seven patients had stable disease. Three partial responses were observed in patients in whom the skin lesions were smaller than 1.5 cm^2. Median duration of respons was 2.5 months and median time to progression for all patients was 1.9 months. In this study topically applied miltefosine for metastatic skin lesions of breast cancer showed modest activity in a relatively heavily pretreated patient population, without serious systemic toxicity. [© 2000 Lippincott Williams & Wilkins.]

Miltefosine was supplied free of charge by Asta Medica AG, Frankfurt, Germany.

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Introduction

Skin metastases of breast cancer are often located at the chest wall and may present as the single metastatic site or may occur concomitantly with metastatic disease at other sites. In patients with isolated skin metastases or skin metastases together with stable disease at other sites, topical application of a cytotoxic drug is attractive as an additive local treatment option, while avoiding further systemic toxicity.[1] Moreover, topical treatment may be of value in skin metastases at the chest wall, in which penetration of systemic chemotherapy is hampered by vascular damage due to previous surgery and/or radiotherapy.

Miltefosine (hexadecylphosphocholine, He-PC) is an alkylphosphocholine. The drug exerts its cytotoxic action by interfering with the metabolism of the cell membrane phospholipids.[2] The cytotoxicity of the agent was shown both after incubation of human leukemic cell lines *in vitro* and after oral administration in chemically induced breast carcinomas in rats *in vivo*.[3] These results stimulated performance of clinical phase I–II studies.[4–6] For the purpose of topical administration He-PC was dissolved in a fixed mixture of alkylglycerols and water, increasing its penetration into the skin. A phase I study in heavily pretreated breast cancer patients with progressive skin metastases showed excellent tolerability of the topical treatment with miltefosine solution at a concentration of 20–80 mg/ml (2–8%), without evident systemic toxicity.[5] Concomitant systemic therapy in that study was not allowed. As the 8% miltefosine solution

showed marked erythema of previously untreated skin, a concentration of 6% was recommended for phase II studies.

In this article we report on the activity and tolerability of a topically applied 6% solution of miltefosine in pretreated patients with progression of skin metastases of breast cancer without progression at other metastatic sites.

Patients and methods

Patients with histologically confirmed breast cancer and progressive skin metastases without progressive disease at other metastatic sites were eligible for this non-randomized single-center study. Concomitant cytotoxic or hormonal therapy was permitted provided it had been started at least 2 months prior to study entry and was continued at an unchanged dose. Further eligibility criteria required a WHO performance status $\leqslant 2$, a life expectancy >3 months, white blood cell count (WBC) $\geqslant 2.5 \times 10^9$/l, platelet count $\geqslant 100 \times 10^9$/l, serum creatinine $\leqslant 177$ μmol/l, alkaline phosphatase $\leqslant 2\times$ the upper limit of normal (UNL) (except in the case of bone metastases), bilirubin $\leqslant 2\times$ UNL and transaminases $\leqslant 4\times$ UNL. Exclusion criteria were: patients requiring radiotherapy of indicator lesions, progressive disease requiring immediate initiation or change of systemic therapy, brain metastases or severe and insufficiently controlled other disease. Informed consent was obtained. The study protocol was approved by the institutional ethics board.

Pretreatment evaluation included: medical history, physical examination, description, measurement and photography of the indicator skin lesions, assessment of other metastatic sites, and hematology and biochemical laboratory analysis including blood cell count, sodium, potassium, Ca, creatinin, AP, ASAT, ALAT, LDH and total protein. During therapy, physical examinations and toxicity assessments were performed at week 1, 2 and 4, and every 4 weeks thereafter. Hematology and chemical laboratory analyses were performed at week 2 and 4, and every 4 weeks thereafter, and objective tumor assessment was performed every 4 weeks. Responses and toxicity were evaluated using standard WHO criteria.

A 6% solution of miltefosine (Asta Medica, Frankfurt, Germany) was applied topically to the skin metastases once daily during the first week and in the absence of toxicity twice daily thereafter. The solution was rubbed smoothly over the affected areas, using one drop of solution per 10 cm^2 of treated skin area. If tolerated, treatment was continued for at least 8 weeks. After reaching complete response, treatment was to be continued for a further 4 weeks. In case of partial response or stable disease it was continued until progression.

Results

Twenty patients were entered into the study. Patient characteristics are depicted in Table 1. One patient was not eligible, because systemic cytotoxic treatment had been discontinued only 18 days before entry in the study. Another patient was formally not evaluable, because miltefosine was stopped after 5 weeks of administration due to early systemic progression and poor tolerability. However, there was no progression of the treated skin lesions. Sixteen patients (80%) had metastatic disease at other sites and received concomitant systemic antitumor therapy. Only three patients had received prior palliative radiotherapy for skin metastases.

Median duration of topical treatment was 10.5 weeks (range 3–46 weeks). Seventeen out of 20 patients could be treated according to the scheduled twice daily application without necessity for dose reduction or delay. Toxicity led to discontinuation of

Table 1. Patient characteristics

Characteristic	
Total no. of patients entered	20
No. of patients evaluable	
for response	18
for toxicity	20
Median age (years)	61
range	43–79
Performance status	
0	8
1	11
unknown	1
Dominant site of disease	
skin only	4
visceral	6
bone	6
soft tissue	4
Prior anticancer therapy	
surgery	19
radiotherapy	19
adjuvant	15
palliative	10
palliative hormonal therapy	19
chemotherapy	11
adjuvant	2
palliative	11
Concomitant anticancer therapy	
none	4
hormonal therapy	9
chemotherapy	7

therapy in three patients after 29, 36 and 51 days: two patients with a large treated skin area of 60 and 100 cm^2, respectively, experienced continuous possible miltefosine-related nausea grade 2 and 1, respectively, another patient stopped treatment due to skin toxicity grade 2. All patients were evaluable for toxicity (Table 2). Grade 3 and 4 toxicity did not occur. Side effects did not require hospitalization. Eleven patients reported adverse skin reactions, mainly grade 1 (nine patients). In patients not receiving concomitant chemotherapy no hematologic or biochemical toxicity was observed. One patient, who did not receive concomitant systemic antitumor therapy, developed anemia and thrombocytopenia grade 3 and elevated serum bilirubin grade 4 due to progressive disease, and died after 46 weeks. One patient on palliative hormonal therapy developed elevated serum transaminases grade 1, another patient with bone metastases showed an elevated serum alkaline phosphatase grade 2.

A partial response was observed in four patients (22%), with a median duration of response of 2.5 months (range 1.0–9.1). Stable disease was noted in seven patients, lasting 1.8–5.9 months with a median of 3.7 months. For the group of evaluable patients, the median time to progression was 1.9 months (range 0.7–9.1 months). A partial response was achieved in three out of six patients (50%) with a maximum size of treated skin lesions less than 1.5 cm^2, compared to only one out of six patients (17%) with a maximum size of treated skin lesions greater than 3.5 cm^2. In the six patients with stable metastatic disease at other sites, a partial response of the skin metastases was seen in three patients and stable disease in the other three patients. Four out of nine patients having progressive systemic disease at other sites also had progression of skin lesions. In the other patient with systemic disease the response of the other sites was not evaluable.

Table 2. Toxicity in 20 evaluable patients

Toxicity	Grade 1 (%)	Grade 2 (%)
Local toxicity		
skin atrophy	4 (20)	–
skin exfoliation	3 (15)	2 (10)
erythematous rash	2 (10)	2 (10)
pruritis	2 (10)	–
pain	3 (15)	–
dry skin	2 (10)	–
teleangiectasis	1 (5)	–
any skin toxicity	9 (45)	2 (10)
Systemic toxicity		
nausea and vomiting	1 (5)	1 (5)
anorexia	1 (5)	–
fatigue	1 (5)	–

Discussion

Most patients with skin metastases of breast cancer will also present with distant metastatic disease, or sooner or later develop such distant metastases.[7] As metastatic breast cancer is still an incurable disease, its treatment should focus on optimal palliation at the expense of minimal toxicity. Although maximal and sometimes aggressive treatment for loco-regional cutaneous disease may be warranted to prevent untreatable and invalidating symptoms of ulceration, bleeding, infection and pain, topical treatment of skin metastases is very attractive because of the ease of self-administration in an outpatient setting and its lack of major systemic toxicity. Topical administered miltefosine has shown activity and a good tolerability in breast cancer. However, while oral adminstered miltefosine appeared feasible and effective in the treatment of visceral leishmaniasis, it lacked activity as an antineoplastic drug.[8,9]

Table 3. Results of topical administration of miltefosine 6% in skin metastases of breast cancer

Author	No. of patients evaluable	Patients with prior palliative chemotherapy	Concomitant anticancer therapy	CR	PR	RR (%)	Reference
Unger[a]	24	20	–	4	3	29	5
Gaafar	17	17	–	0	7	41	10
Terwogt	30	25	–	7	6	43	11
Clavel	23	23	+	0	8	35	12
Khayat	20	20	20	2	6	40	13
Clive	14	+	7	0	7	50	14
Clive	25	19	15	1	2	12	15
Smorenburg	18	11	16	0	4	22	this study

[a]This study used miltefosine at a concentration of 2–8%

Treatment results of eight phase I–II studies using topically applied miltefosine for skin metastases in patients with breast cancer are summarized in Table 3. The median response rate in these studies is 38% (range 12–50%). In our study, a 6% solution of miltefosine showed modest activity, with four partial responses and additionally seven stable diseases. The response rate of 22% contrasts unfavorably to those reported in other studies.[5,10–15] This may be due to more advanced disease in our study population, since 16 out of 20 patients also had distant metastatic disease (of whom six had visceral disease). It may also be due to more extensive prior systemic anticancer therapy which consisted of two or more lines of palliative hormonal or cytotoxic therapy in 12 and six of our patients, respectively. A higher response rate was indeed suggested in patients in whom the skin lesions were smaller than 1.5 cm^2 and in patients without systemic progressive disease. In an overview analysis of topical miltefosine in metastatic breast cancer, Sinderman *et al.* identified size of tumor lesions and depth of infiltration as significant prognostic factors for tumor response.[16] The present study confirmed the good tolerability as seen in other clinical studies, with mild skin reactions and gastrointestinal toxicity in 12 and two patients, respectively.

In conclusion, topically administered miltefosine may effectively control skin metastases (especially small lesions) in patients with metastatic breast cancer, without inconvenient side effects or hospitalized care.

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