Cutaneous breast cancer metastases successfully treated using an oxygen flow assisted administration of methotrexate (OFAMTX5%)

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Short report

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Abstract

Introduction: Cutaneous metastases of breast cancer (CMOBC) remain a therapeutic challenge. Recently, oxygen flow assisted topical administration of methotrexate 3% (OFAMTX5%) was proven an efficacious alternative treatment for extramammary Paget's disease, an in situ mammary adenocarcinoma. Aim: To evaluate the efficacy and tolerance of OFAMTX5% for the treatment of CMOBC. Materials and methods: A patient with triple negative breast cancer presented with biopsy proven CMOBC. Two weekly sessions were given for 2 weeks with OFAMTX5% on a site of approximately 40 cm 2 . Skin biopsies were performed before and 2 months after procedure. Results: Tolerance was excellent with no pain sensations. Two months post procedure the treated area presented a postinflammatory hyperpigmentation. No residual metastases were evidenced on the control skin biopsy. Discussion: In selected cases of CMOBC OFAMTX5% can represent a non-painfull and efficacious treatment alternative. Larger series should evaluate the place of OFAMTX5% for the treatment of CMOBC.

Introduction

Cutaneous metastases of breast cancer (CMOBC) may occur in up to 1/3 of patients and are usually a sign of poor prognosis (1).. They present an important impact on the quality of life and can present difficult therapeutic challenges. Treatments can be either systemic but in patients with no signs of residual internal breast cancer lesions, topical approaches may be favored to avoid systemic adverse effects.

Skin-directed treatment options for CMOBC include radiotherapy (2), surgical excision (3), electrochemotherapy (4), topical imiquimod (3,5–7), either as monotherapies or combination therapies (6,8), cryotherapy (8), 5-fluorouracil (5-FU) (8), photodynamic therapy (9–11) and topical applications of miltefosine (2,12,13).

Oxygen flow assisted topical administration of methotrexate (OFAMTX) is a recently described technique permitting permeation of the epidermis for molecules with a high molecular weight, that do not penetrate the skin under normal circumstances (14). This technique effectively treated extramammary Paget's disease (EMPD), a chronically evolving and recurrent intraepidermal adenocarcinoma (14). Furthermore, as methotrexate is used as component of some breast cancer chemotherapy (15), OFAMTX was evaluated for treating superficial CMOBC.

Case Report

A 51-year-old patient presented a suspect mass of her right breast, suggesting a right carcinomatous mastitis with axillary lymph node extension. MRI confirmed a lesion of the entire right breast, 8 cm in size, with infiltration of the nipple, accompanied by mastitis and axillary lymph node infiltration. A biopsy revealed an invasive ductal carcinoma, grade III of Bloom, triple negative (Estrogen Receptor -, Progesterone Receptor - and HER-2 -), with a high proliferation index (Ki67: 63%). Axillary lymph node

needle aspiration was positive. TAP scanner and bone scintigraphy was negative for distant metastasis. A neo-adjuvant chemotherapy was instaured with 4 courses of epirubicin and cyclophosphamide (75 mg/m^2 and 500 mg/m^2 every 15 days), followed by 12 weekly paclitaxel courses (80 mg/m^2). The overall tolerance was very good. One month later, a right mastectomy and a sentinel lymph node were performed. Histology revealed multiple scattered lymphovascular embolizations involving around 20% of the mastectomy, but no initial tumor lesion was found. There was an infiltration of 2 out of 3 lymph nodes, with micrometastases of 1.8 and 5 mm. Immunohistochemistry confirmed the triple negative character. Histological staging was T1cN1cMx.

Two weeks following surgery, isolated macular and slightly infiltrated erythematous lesions were evidenced in the near vicinity of the mastectomy scar. A skin biopsy revealed a cutaneous infiltration with breast carcinoma, triple negative, with a Ki67 of 80%. Subsequently a chemotherapy with capecitabine (1250 mg/m^2, 2x/day, 2 weeks/3) was started and adjuvant radiotherapy was administered (50 Gy, 25 sessions of 2 Gy) on the right chest wall and the supraclavicular region, followed by a boost on the scar and skin metastases (16 Gy, 8 sessions of 2 Gy). Five months later, new cutaneous metastases appeared, presenting as Velpeau's nodules on the edge of the lower fields of the radiotherapy area (Fig. 1a). PET scanning remained negative for at distance lesions and at lymph node level. As the PET scanner did not reveal any internal lesions a topical treatment with OFAMTX5% was applied (2x/week for 2 weeks) to the lesions. The patient gave written informed consent for the off-label use of this technique. A biopsy before OFAMTX5% treatment revealed again a superficial and deep dermal infiltration of neoplastic mammary carcinoma cells (Fig. 1b) with Ker7 immunohistochemical expression (Fig. 1c). Two months following procedure, a postinflammatory pigmentation was observed (Fig. 1d) but clinically there were no infiltrated lesions evidenced. A control skin biopsy was performed and revealed a total remission (Fig. 1e). The patient considered this treatment as highly comfortable as she did not experience any pain sensations and no crusting or oozing post procedures. At the last control visit, three months later, a post inflammatory hyperpigmentation was present but there was still no clinical evidence of local recurrence of cutaneous metastases.

Discussion

The treatment of CMOBC remains difficult and, unfortunately, treatment options do usually not represent long-term solutions. Hence, in this palliative setting, there is a medical need for patient-friendly, not pain-full, skin-directed treatments with a good local tolerance.

This case demonstrated the possibility of treating superficial CMOBC with OFAMTX5% in a painless manner, whilst continuing chemotherapy. OFAMTX5% could be considered as alternative skin-directed therapy such as miltefosine, imiquimod, 5-FU and photodynamic therapy. The principal skin-directed options are discussed hereunder, excluding electrochemotherapy and radiotherapy.

Miltefosine 6% solution is a topical cytostatic agent. Miltefosine interacts with lipids, inhibits cytochrome c-oxidase and leads to an apoptosis-like cell death. Miltefosine was applied to the skin using 2

drops/10 cm^2 for often pretreated CMOBC in 25 patients for a median of 14 weeks (range 2-164). Grade 1 and 3 cutaneous toxicities were noted 28% and 16% of the patients, respectively, the latter requiring dose adjustments. A response was observed in 36% of the patients with 1 complete, 2 partial and 6 minor responses. Stable disease was observed in 44% of the patients and progressive disease in 20%. Superficial lesions or lesion less than 2 cm in diameter were the most likely to respond (12).

Later, a double-blind, placebo-controlled, multicenter phase III study evaluated in a cohort of 52 patients with CMOBC with superficial or flat skin lesions with < or = 1 cm of estimated depth, the efficacy and tolerance of 6% miltefosine solution (2 drops/10 cm^2), once daily during the first week and twice daily until treatment failure. The time to treatment failure was significantly superior for miltefosine compared to placebo 56 days versus 21 days, respectively. Cutaneous reactions were more frequent in the miltefosine group, although, when present, were well tolerated and only occasionally required treatment interruption (13).

Imiquimod induces endogenous production of interferon mediated by the TLR7 pathway. Imiquimod is a recognized treatment for actinic keratosis and superficial basal cell carcinoma, and used off-label for in situ melanoma and EMPD. Imiquimod 5% cream in combination with cryotherapy was administered in one patient with CMOBC, 3–5 per week, every 3 weeks with initial shrinking of the lesions (8).

A prospective study evaluated in 10 patients with CMOBC the local tumor response rate using topical imiquimod, applied 5 d/week for 8 weeks. Grade 1 to 2 transient local and systemic side effects were observed. A partial response was noted in 20%. Histology revealed tumor regression revealed by changes in the tumor lymphocytic infiltrate and locally produced cytokines (5).

Another paper presented the case of a 26 years-old woman with CMOBC who received topical imiquimod 3x/week for over 4 months, whilst continuing systemic chemotherapy, experiencing a reduction of the lesion thickness, following by a size reduction with no reported adverse effects (3).

A single arm phase 2 clinical study treated 15 patients with CMBOC with 4 days treatment courses for 12 weeks of imiquimod cream 5% while continuing paclitaxel treatment 100 mg/m^2. Combination therapy was associated with low-grade toxic effects. Of 358 adverse events 330 (92%) were grades 1 and 2. Five (36%) patients achieved a complete response and another 5 (36%) were partial responders for an overall response rate of 72% (10/14). The response duration was limited. Pretreatment levels of programmed death-1 (PD-1) + peripheral blood T cells (PD-1 + CD4 + and PD-1 + CD8 + and monocytic myeloid derived suppressor cells greater than controls were predictive of suboptimal clinical responses (6).

Using transcriptomic profiling it could be demonstrated that responsiveness to imiquimod therapy for CMOBC with a durable clinical response depended on a permissive microenvironment, substantiated by the upregulation of transcripts encoding for molecules involved in leukocyte adhesion and migration, cytotoxic functions, and antigen presentation. In responding patients, Imiquimod triggered a strong T-helper-1 (Th-1)/cytotoxic immune response, ultimately mediating tumor destruction (7).

5-fluorouracil belongs to the class of antimetabolites and functions like other analogues of pyrimidin. 5-FU 5% cream 2x/d in combination with cryotherapy was used for 4 months with good but transient clinical responses and acceptable local adverse reactions in 2 patients with CMOBC (8).

Photodynamic therapy (PDT), either using topically or intravenously administered photosensitizers, has also been used for CMOBC. In a series of 37 patients with CMOBC, intravenous photofrin II PDT was performed, with 5 complete responses, 13 partial responses and 19 non-responders. The extension and the size of the lesions were the most important predictive parameters for successful responses (9). Topical meso-tetra-porphon (TPPS4)-PDT used in 9 patients with CMOBC revealed 3 complete, 4 partial and 2 non-responders (10). Two elderly patients with CMOBC revealed partial responses after 2 weekly methylaminolevulinate (MAL)-PDT sessions. At 4 weeks, histology showed a clearance of tumor infiltration of the dermis and superficial hypodermis. Unfortunately, persistent tumor nests were still observed in the deep hypodermis (11).

In general, skin-directed therapies for CMOBC, including OFAMTX, could be helpful in superficial lesions regardless of the size. Combination with systemic therapy probably increases the efficacy of skin-directed therapies. Combining skin-directed therapies with different action mechanisms, ie immunostimulatory and antimetabolic, probably further increases effectiveness.

In conclusion, OFAMTX5% was an effective and well-tolerated treatment for superficial CMOBC. More cases will have to be treated in order to determine optimal treatment regimens and, in fine, its place in the armamentarium against CMOBC.

Declarations

Ethical Approval and Consent to participate: The patient was informed on all the procedures and consented to participate.

Consent for publication: The patient provided written consent for publication of her clinical images.

Availability of supporting data: Not applicable.

Competing interests: All the authors declare no competing interests.

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Authors' contributions: GJ, EG, PQ, MAR, PC, EL GJ and AFN all participated in the design of the study and of the interpretation of results as well as in the discussion.

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References

1. Strickley JD, Jenson AB, Jung JY. Cutaneous metastasis. Hematol Oncol Clin North Am 2019;33:173-197.
2. Varol U, Yildiz I, Alacacioglu A, Uslu R. Anticancer therapy for breast cancer patients with skin metastases refractory to conventional treatments. Asian Pac J Cancer Prev 2014;15:1885-7.
3. Henriques L, Palumbo M, Guay MP, Bahoric B, Basik M, Kavan P, Batist G. Imiquimod in the treatment of breast cancer skin metastasis. J Clin Oncol 2014;32:e22-5.
4. Wichtowski M, Murawa D, Czarnecki R, Piechocki J, Nowecki Z, Witkiewicz W. Electrochemotherapy in the treatment of breast cancer metastasis to the skin and subcutaneous tissue - multicenter experience. Oncol Res Treat 2019;42:47-51.
5. Adams S, Kozhaya L, Martiniuk F, Meng TC, Chiriboga L, Liebes L, Hochman T, Shuman N, Axelrod D, Speyer J, Novik Y, Tiersten A, Goldberg JD, Formenti SC, Bhardwaj N, Unutmaz D, Demaria S. Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer. Clin Cancer Res 2012;18:6748-57.
6. Salazar LG, Lu H, Reichow JL, Childs JS, Coveler AL, Higgins DM, Waisman J, Allison KH, Dang Y, Disis ML. Topical imiquimod plus nab-paclitaxel for breast cancer cutaneous metastases: a phase 2 clinical trial. JAMA Oncol 2017;3:969-73.
7. Rozenblit M, Hendrickx W, Heguy A, Chiriboga L, Loomis C, Ray K, Darvishian F, Egeblad M, Demaria S, Marincola FM, Bedognetti D, Adams S. Transcriptomic profiles conducive to immune-mediated tumor rejection in human breast cancer skin metastases treated with Imiquimod. Sci Rep 2019;9:8572.
8. Krishnasamy SR, Almazan TH, Suero-Abreu GA, Jung JY. Successful treatment of cutaneous metastatic breast cancer with topical treatments that potentially synergize with systemic therapy: A case series. JAAD Case Rep 2018;4:711-715.
9. Khan SA, Dougherty TJ, Mang TS. An evaluation of photodynamic therapy in the management of cutaneous metastases of breast cancer. Eur J Cancer 1993;29A:1686-90.
10. Lapes M, Petera J, Jirsa M. Photodynamic therapy of cutaneous metastases of breast cancer after local application of meso-tetra-(para-sulphophenyl)-porphin (TPPS4). J Photochem Photobiol B. 1996;36:205-7.
11. Wauters O, Caucanas M, Richert B, Dezfoulian B, Nikkels AF. The clinical relevance of off-label photodynamic therapy in onco-dermatology. J Clin Dermatol 2010;1:1-11 http://hdl.handle.net/2268/161519

12. Clive S, Gardiner J, Leonard RC. Miltefosine as a topical treatment for cutaneous metastases in breast carcinoma. Cancer Chemother Pharmacol 1999;44 Suppl:S29-30.
13. Leonard R, Hardy J, van Tienhoven G, Houston S, Simmonds P, David M, Mansi J. Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. J Clin Oncol 2001;19:4150-9.
14. Lebas E, Chapelier C, Quatresooz P, Seidel L, Nikkels AF. Exploratory assessment of oxygen flow-assisted cutaneous administration of methotrexate for superficial basal cell carcinoma, mycosis fungoides, and extramammary Paget disease. J Invest Dermatol 2019 Sep 9. pii: S0022-202X(19)33215-4.
15. Orlando L, Schiavone P, Calvani N, Fedele P, Goldhirsch A, Cinieri S. Response of extensive breast cancer skin metastases to rechallenge with trastuzumab together with low-dose chemotherapy and insulin. Tumori 2016;102(Suppl. 2).

Figures

Figure 1

a: CMOBC clinical aspect before treatment, b: histology evidencing superficial tumoral infiltrate in the dermis, c: Keratine 7 immunohistochemical evidencing of tumor cells, d: clinical aspect 2 months post OFAMTX procedure, 1 e: control biopsy revealing no residual tumor nests.