Successful treatment of cutaneous metastatic breast cancer with topical treatments that potentially synergize with systemic therapy: A case series

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INTRODUCTION

Breast cancer is the second most common malignancy after melanoma to metastasize to skin.[1] Approximately 30% of individuals with metastatic breast cancer (MBC) go on to have cutaneous metastases, frequently presenting as firm nodules, diffuse infiltrative or ulcerative lesions, often in proximity to an old mastectomy scar.[2,3] Cutaneous metastases of breast cancer (CMOBC) is a therapeutic challenge and is associated with increased morbidity. Progression of disease often results in severe pain, chest wall ulceration, bleeding, and superinfection.[2] Optimal management of these highly morbid lesions is an active area of investigation. Apart from improving quality of life, recent evidence suggests that skin-directed treatment of CMOBC with topical imiquimod can provide durable systemic responses that prolong survival.[3,4]

We present 3 cases of CMOBC treated with cryotherapy in combination with either topical fluorouracil 5% (5FU) or topical imiquimod. All patients had striking responses both locally and systemically. We hypothesize that there may be a role for topical therapy in palliation of CMOBC. Current evidence suggests there may be synergy between systemic therapies and the antitumor response induced by skin-directed therapies: cryotherapy generating an in situ vaccination of tumor and topical 5FU or imiquimod generating and sustaining a favorable inflammatory milieu.[3,5-8] Although large-scale controlled studies are needed to determine if skin-directed therapy plays a role in the treatment of MBC, these results suggest combined therapy may be effective for CMOBC.

Abbreviations used:

5FU:	fluorouracil 5%
CMOBC:	cutaneous metastases of breast cancer
MBC:	metastatic breast cancer
TLR7:	toll-like receptor 7

CASE PRESENTATIONS

Patient 1 is a woman in her 60s with ER^+, $HER2^+$ MBC referred for treatment evaluation of CMOBC. Prior treatments included mastectomy, radiation, multiple lines of chemotherapy, and targeted and endocrine therapy. On presentation, her treatment regimen included letrozole and radiation to left axillary lymph nodes. Despite these treatments, she required frequent transfusions and multiple daily dressing changes because of bleeding from

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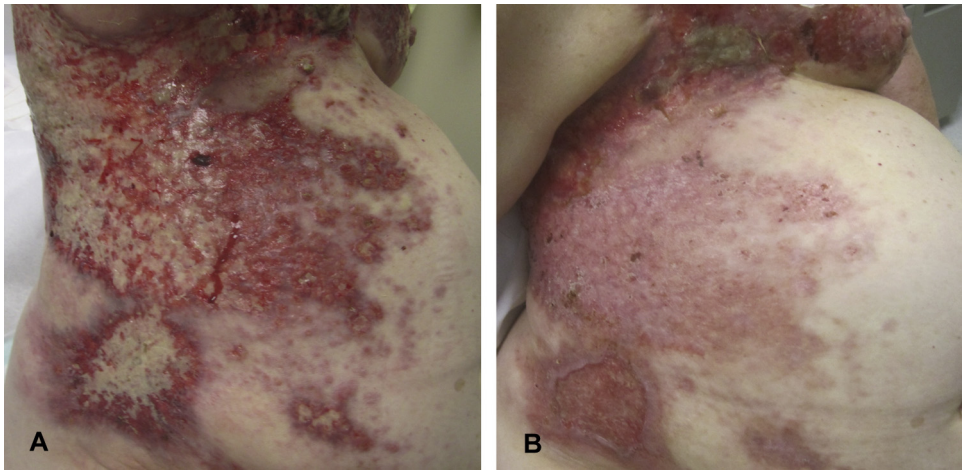

Fig 1. Clinical response of patient 1 to treatment with 5FU and cryotherapy. **A**, Clinical image, initial presentation. Numerous eroded, exophytic, bleeding, and friable plaques affecting the back, chest, and abdomen of patient 1 before treatment with 5FU and cryotherapy. **B**, Clinical image, 4-month follow-up. Significant clinical response, most prominent over the right side of the abdomen of patient 1 after 4 months of skin-directed treatment combined with systemic letrozole and radiation.

her CMOBC. Physical examination found extensive friable metastases on her trunk (Fig 1, *A*). Treatment with 5FU cream twice daily to her right lower abdomen was initiated with reduction in pain, bleeding, and drainage within the first week. Treatment with cryotherapy every 2 weeks to 4 to 6 areas was subsequently started. After just 2 cryotherapy treatments, her lesions healed appreciably, only requiring dressing changes every 2 days. She completed a 4-month course of topical 5FU and cryotherapy with dramatic cutaneous response, most prominent in the area treated with 5FU (right lower abdomen; Fig, 1, *B*). She was continued on letrozole and palliative radiation with sustained improvement at 6 months.

Patient 2 is a woman in her 60s with metastatic triple negative breast cancer. Despite treatment with multiple chemotherapeutics and radiation, her disease progressed prompting initiation of irinotecan salvage chemotherapy and referral to the dermatology department for additional treatment recommendations. On examination, she had cutaneous metastases limited to the right side of her chest and upper arm (Fig 2, *A*). Treatment with topical imiquimod daily and cryotherapy to 2 to 12 lesions every 3 weeks was started. Despite initial resolution of several lesions, within 1 month she had progressive chest wall involvement, prompting addition of ixabepilone, another chemotherapeutic agent. Regression was noted after the first cycle of ixabepilone, with near complete resolution after the third cycle (Fig 2, *B*), at which point she had received 3 months of skin-directed treatment.

Patient 3 is a woman in her 30s with recurrent metastatic HER2^{+} MBC who presented for treatment of CMOBC. Neoadjuvant chemotherapy with trastuzumab and lapatinib and a right-sided, skin-sparing mastectomy followed by 1 year of trastuzumab sent her into remission. Two years later, local recurrence developed. Examination found an ulcerating plaque at her mastectomy site. Treatment with 5FU twice daily was initiated with immediate reduction in drainage and bleeding. Cryotherapy every 2 weeks to localized areas of the tumor was subsequently started. Despite initial improvement, her localized tumor completely ulcerated and rapidly progressive cutaneous involvement developed (Fig 3, *A*) along with nodal and brain metastases. Brain radiation and treatment with docetaxel, pertuzumab, and trastuzumab was initiated. With continued topical therapy, her lesions noticeably improved after 1 cycle of chemotherapy and responded remarkably after 4 cycles. Within 4 months of combined systemic and skin-directed therapy, she achieved a full clinical response with resolution of systemic and cutaneous metastases (Fig 3, *B*). She continued on pertuzumab and trastuzumab maintenance therapy without evidence of recurrence at 19 months.

DISCUSSION

Here we describe 3 patients with CMOBC in whom combined skin-directed and systemic therapies produced dramatic clinical responses. In the authors experience, this uncharacteristic response to systemic therapy alone, particularly