Case Report

rare tumors

Rare Tumors
Volume 13: 1–5

DOI: 10.1177/2036361320975748
journals.sagepub.com/home/rtu
SAGE

A case report of imiquimod topical therapy as treatment for cutaneous metastasis of breast cancer

Anthony L Nguyen[1], Esther G Chong[2], Joanne Lee[3], Saied Mirshahidi[4] and Hamid Mirshahidi[1]

Abstract

Cutaneous metastasis of breast cancer carries a poor prognosis, invokes a poor quality of life, and increases mortality by raising one's risk of bleeding and infection. Currently, options for treatment are systemic chemotherapy, surgical resection and radiation. These treatments are invasive and can have toxic side effects. A 50-year-old African-American woman with stage IV breast cancer with cutaneous metastasis to the left anterior chest and left supraclavicular area was successfully treated with topical imiquimod. She experienced improvement in appearance and symptoms within several months of starting treatment, resulting in near resolution of her cutaneous metastasis. Imiquimod is currently approved for several cutaneous conditions and has the potential to treat cutaneous metastasis of breast cancer.

Keywords

Imiquimod, cutaneous metastasis, topical, therapy

Date received: 30 June 2020; accepted: 2 November 2020

Introduction

Breast cancer is the most common cancer occurring in women. It originates from mammary ducts, which are ectodermal appendages, and so commonly leads to skin metastases in up to 24% of patients.[1] Often, skin metastasis will occur after subtotal mastectomy and presents as ulcerations, diffuse infiltrative lesions, or nodules in the vicinity of the tumor, chest wall, or the skin over residual breast tissue. It carries a poor prognosis, significant decrease in quality of life, and increases the risk of infection and bleeding. Even after usual treatments including surgical resection and radiation after resection, tumor recurrence is common, which is requiring new treatment strategies.[2] Imiquimod, a Toll-like receptor (TLR)-7 agonist has been Food and Drug Administration (FDA) approved for genital warts, basal cell carcinoma, and actinic keratosis.[3] In this report, we describe a case of a patient with an extensive history of stage IV breast cancer with skin metastasis, successfully treated with imiquimod.

Case description

A 50-year-old African American woman was diagnosed with left breast ductal carcinoma in situ (DCIS) in 1999 and was treated with a left total mastectomy followed by a left breast implant. In 2005, she developed lymphadenopathy

[1]Division of Medical Oncology and Hematology, Department of Medicine, Loma Linda University Medical Center, Loma Linda, CA, USA
[2]Department of Medicine, Loma Linda University Medical Center, Loma Linda, CA, USA
[3]Loma Linda University School of Medicine, Loma Linda, CA, USA
[4]Loma Linda University Cancer Center Biospecimen Laboratory, Department of Microbiology, Loma Linda University School of Medicine, Loma Linda, CA, USA

Corresponding author:
Hamid Mirshahidi, Division of Medical Oncology and Hematology, Department of Medicine, Loma Linda University Cancer Center, 11175 Campus Street, CSP 11015, Loma Linda, CA 92354, USA.
Email: HMirshah@llu.edu

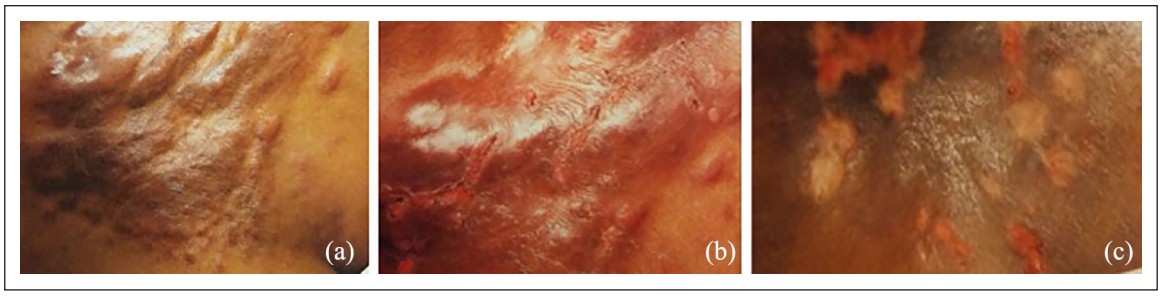

Figure 1. Cutaneous metastasis of breast cancer at various intervals post-topical imiquimod therapy: initial hypertrophic, hyperpigmented, thick plaque-like lesions over left anterior chest and left supraclavicular area (a), 2 months after starting treatment, thickness of lesions decreased (b), and 4 months after starting treatment, hypertrophic lesions resolved, leaving only macular scars (c).

and was found to have recurrence and metastasis in the left supraclavicular, axillary, hilar, and mediastinal lymph nodes and was diagnosed with stage IV breast adenocarcinoma. These lesions were biopsied and found to be Estrogen Receptor (ER) positive, Progesterone Receptor (PR) positive, and Human Epidermal Growth Receptor 2 (HER2) negative by fluorescent in situ hybridization (FISH). She then completed five cycles of chemotherapy with docetaxel and cyclophosphamide, along with consolidation treatment with radiation to her supraclavicular area and axilla. During these treatments, she portrayed good clinical and radiographic response. Her disease was continuously monitored with Cancer Antigen 27-29 (CA 27-29) levels and positron emission tomography–computed tomography (PET-CT). She was treated with anastrozole after radiation for 18 months without evidence of recurrence, but it was subsequently discontinued due to progression of metastatic disease. She was then started on fulvestrant for 1 year with adequate response on PET-CT by April 2008. However, she decided to stop further treatment in order to seek alternative natural treatments. Unfortunately, in January 2009, she noted skin hardening, pain, and hyperpigmentation over her left chest wall, along with increasing lymphatic masses in her left neck and left supraclavicular area. PET-CT demonstrated cervical, supraclavicular, mediastinal and axillary lymphadenopathy with increased uptake in the sternum and left chest wall related to the tumor, and also in her left upper lung. She described the lesions as hard, painful, burning, and ulcerative. Her skin lesions were biopsied and confirmed to be infiltrating adenocarcinoma, ER positive, PR negative, HER2 negative. Docetaxel was restarted for seven cycles and followed by capecitabine for five cycles. She had radiographic improvement on PET-CT but continued to have progression of skin lesions.

To treat her metastatic skin lesion to the upper left chest wall and left supraclavicular area, the patient requested topical treatment with imiquimod therapy, after reading about its potential efficacy for chest wall metastases in an article. After discussion with dermatology, a consultation was obtained and she was started on topical imiquimod 5% cream to her skin lesions twice per day for 5 days a week. Additionally, she was started on letrozole concurrently with topical imiquimod after an unsuccessful short trial of gemcitabine. As demonstrated in Figure 1(a) to (c), she had progressive and gradual improvement and regression of her skin lesions within 4 months of starting topical imiquimod cream. Given her clinical improvement, radiation therapy was no longer indicated.

The lesions decreased in size, thickness, and pigmentation, with resolution of ulceration and pain. Following initial improvement of skin lesions after 4 months of use, she started to use imiquimod as needed, according to her symptoms and size of her lesions while undergoing systemic treatment. Unfortunately, the patient continued to develop metastatic disease to the brain, liver, and lungs despite further systemic treatment with fulvestrant, anastrozole, paclitaxel, everolimus, and exemestane. She eventually succumbed to her disease and passed away 14 years after her initial diagnosis.

Discussion

This case adds to the growing body of literature demonstrating that topical imiquimod cream is a potential treatment option for cutaneous metastasis of breast cancer. The Food and Drug Administration (FDA) approved imiquimod's use for treatment of genital warts in 1999 and subsequently approved its use for treatment of basal cell carcinoma and actinic keratosis in 2004.[4] Since then, imiquimod has been used for treatments of squamous cell carcinoma, herpes simplex virus, and intraepidermal carcinoma, as well as other skin cancers and various fungal infections. Its clinical success is attributed due to its antitumor activity. Imiquimod's exact mechanism of action is yet to be elucidated but studies suggest that imiquimod activates the innate and the adaptive immune systems both directly and indirectly. Its direct action occurs by binding to toll-like receptors, which seems to activate both the extrinsic and the intrinsic pathways of apoptosis. This is mediated by activation of caspase proteases, upregulation of

proapoptotic proteins such as *Fas*, Bax, and Bak, and downregulation antiapoptotic proteins such as Bcl-2 and Bcl-XL.[4] At the same time, imiquimod's binding to TLR-7 receptors present on dendritic cells, macrophages, and monocytes leads to the release of pro-inflammatory cytokines such as IFN- α and TNF- α among others, which in turn increase the levels of cytotoxic T cells and natural killer cells.[5] Additionally, imiquimod has been shown to enhance the maturation, migration, and function of Langerhans cells which allows for a more specific T cell immune response.[6]

There have been other reported cases of using imiquimod for breast cancer metastases in literature, however the discussed case in this report demonstrates the longest interval between initial diagnosis of the patient's primary breast cancer and eventual cutaneous metastasis–10 years. The first description of the use of topical imiquimod in cutaneous metastasis of breast cancer was described by Hengge et al.[1] who described its use in two patients who developed cutaneous metastasis 9 months after surgical resection, adjuvant chemotherapy, and radiation. One patient's disease was $ER^+/PR^+/Her2^+$ while the other had $ER^-/PR^-/Her2^-$ disease. Skin biopsies of both patients confirmed invasive carcinoma cells, and both patients were treated with topical imiquimod five times per week for 6 months with resolution of lesions grossly and histologically. The proposed mechanism of imiquimod at that time was through induction of maturation and migration of cutaneous dendritic cells, increasing antigen presentation through cytokines, which leads to a Cluster of Differentiation Eight $(CD8)^+$ T-cell mediated antitumor response to cutaneous carcinoma cells.

Another case report by Henriques et al.[2] described a patient a 26-year-old patient with $ER^+/PR^+/Her\text{-}2^-$ T2N3 invasive ductal breast cancer treated with neoadjuvant chemotherapy followed by radical mastectomy and adjuvant radiation. The patient was treated with tamoxifen and then with letrozole and goserelin for maintenance therapy. Three years later, she developed left axillary swelling and lymph node biopsy revealed $ER^-/PR^-/Her2^+$ carcinoma. She was treated with adjuvant chemotherapy and received maintenance therapy with trastuzumab. While on the maintenance therapy, she progressed to developing metastatic skin lesions to the left axilla with lymphadenopathy with biopsy revealing invasive ductal carcinoma $ER^-/PR^-/Her2^-$. She was treated with radiotherapy and chemotherapy, however the skin lesions continued to progress causing pain. Topical imiquimod 5% was applied three times per week, which decreased the thickness and intensity of skin lesions within a week of medication initiation. After 4 months of therapy, the lesions regressed significantly. Given imiquimod's efficacy in a variety of different cutaneous metastases, the authors postulated that the immunomodulatory effects of imiquimod may be nonspecific yet intense.

Additionally, a case series by Krishnasamy et al.[7] described three cases of successful treatments of cutaneous metastasis of breast cancer with a combination of cryotherapy and either topical fluorouracil 5% or topical imiquimod. One of the three patients presented with cutaneous lesions following extensive chemoradiation of breast cancer. She was initiated on topical imiquimod daily and cryotherapy every 3 weeks along with salvage chemotherapy and was found to have near complete resolution after 3 months of treatment. The authors attributed the unusually rapid response of cutaneous metastasis after only four cycles of chemotherapy to the immunomodulatory effects of imiquimod and cryotherapy, suggesting the beneficial role of concurrent cryotherapy and topical immunomodulators in management of cutaneous metastasis of breast cancer.

The first preclinical trial evaluating the clinical efficacy of imiquimod was conducted by Dewan et al.[8] in which the researchers injected TSA mouse breast carcinoma cells into mice, applied topical imiquimod concurrently with radiation and cyclophosphamide, and monitored the mice for tumor growth and survival. The authors found that treatment with imiquimod significantly inhibited tumor growth by increasing tumor infiltration by $CD11c^+$, $CD4^+$, and $CD8^+$ cells. In addition, it was found that imiquimod administration with radiotherapy significantly potentiated the therapeutic effects of both than compared to either alone, and also resulted in decreased secondary tumor growth outside of the radiation field. The addition of cyclophosphamide to imiquimod showed further decrease in tumor progression as well as recurrence. The data presented showed promise in topical imiquimod's potential in becoming a valuable adjuvant therapy.

This preclinical trial was followed by the first phase II prospective trial by Adams et al.[9] who enrolled 10 women with refractory breast cancer skin metastases on concurrent systemic therapy. The subjects used topical 5% imiquimod for 5 days per week for 8 weeks, which resulted in a 20% clinical response rate without significant adverse effects. Skin biopsies of two subjects with a clinical response showed histologic changes suggestive of a local anti-tumor response. Immunohistological evaluation in this study revealed an immune-mediated response with Interferon-α (IFN-α) and IFN-γ signaling, increased response by Th1 and CD8 T-cells to the tumor, myeloid dendritic cell and plasmacytoid dendritic cell response, and decreased immunosuppression leading to an immune-mediated local antitumor response. In contrast to previously published literature, biopsies after 8 weeks of imiquimod treatment did not show a consistent increase in plasmacytoid dendritic cells. Levels of other immunomodulating molecules previously thought to be involved in imiquimod's mechanism of action such as IFN-γ, IL-6, and IL-10 did not show a significant change between pre-treatment and post-treatment as well. Given the small number of patients, more

clinical trials are needed to derive significance in aforementioned findings.

With improving evidence of imiquimod's local immunomodulatory effects, Salazar et al.[10] conducted a phase 2 clinical trial investigating the role of imiquimod in treating recurrent breast cancer of the chest wall. Since taxanes also have immunomodulatory effects, weekly intravenous albumin-bound paclitaxel (nab-paclitaxel) was used with topical imiquimod to treat patients with breast cancer with treatment-refractory chest wall disease. Fifteen patients with stage IV disease were enrolled and received topical imiquimod daily for 4 days consecutively once per day for 4 consecutive days on days 1 through 4, 8 through 11, 15 through 18, and 22 through 25 of a 28-day cycle for 12 weeks, in addition to intravenous administration of albumin bound paclitaxel (nab-paclitaxel) on days 1, 8, and 15, and repeated every 28 days over a 12-week period. Among 15 study participants, 5 patients achieved clinical response and 5 patients achieved partial response; the combination of topical and systemic immunotherapy was shown to achieve a clinical response rate higher than conventional chemotherapy alone. In addition, the study found that higher levels of pretreatment Programmed Cell Death Protein 1 $(PD\text{-}1)^+$ T cells, indicating T-cell exhaustion or defects, were associated with suboptimal response to chemoimmunotherapy, suggesting the potential of PD-1 blockade in achieving even greater clinical response. Clinical trials studying the anti-tumor effects of Imiquimod with taxane therapy are currently underway (NCT00821964).

Several case reports have shown clinical improvement with topical imiquimod therapy for other cutaneous malignancies, such as melanoma.[11,12] Additionally, there has been growing interest in using topical imiquimod in conjunction with immunotherapy[13] and currently a clinical trial studying the effects of combination therapy with imiquimod and PD-1 inhibitor immunotherapy for stage IIIB-IV melanoma (NCT03276832).

Conclusion

Overall, evidence points to the ability of imiquimod to induce a pro-immunogenic tumor microenvironment. In our case, the patient reported improved pain, and ultimately, resolution of lesion size, thickness, and ulcerations after 4 months of regular use. When imiquimod therapy was started, she was on letrozole, an aromatase inhibitor, which could have contributed to her disease regression. However, the previous systemic treatments, which led to clinical and radiographic improvement, did not coincide with improvement of skin lesions. Even late in her disease with recurrence of advanced metastasis, her skin lesions remained controlled on imiquimod, while chemotherapeutic and hormonal treatments failed to control her metastatic disease radiographically and clinically.

Further histological and molecular studies are needed to elucidate the exact anti-tumor mechanisms of imiquimod. Despite limited research and data, topical imiquimod holds excellent promise as a treatment option for cutaneous metastasis of breast cancer in conjunction with systemic immunomodulatory therapies. Recent studies combining imiquimod with radiation therapy and systemic chemotherapy shows promise in promoting pro-immunogenic antitumor effects through synergistic mechanisms.[5] Larger studies need to be completed with imiquimod in conjunction with chemotherapy, radiation therapy and immune therapy to prove its overall effectiveness.

Author contributions

EC and JL designed the report and created drafts of the paper. AN performed clinical examination and designed the report. SM and HM designed the report. All authors reviewed and edited the manuscript and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was not required, as this case report documents and studies patient's disease course and did not require the patient to be protected from any interventions by the authors

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD

Esther G Chong https://orcid.org/0000-0002-0508-9521

References

1. Hengge UR, Roth S and Tannapfel A. Topical imiquimod to treat recurrent breast cancer. *Breast Cancer Res Treat* 2005; 94(1): 93–94.
2. Henriques L, Palumbo M, Guay MP, et al. Imiquimod in the treatment of breast cancer skin metastasis. *J Clin Oncol* 2014; 32(8): e22–e25.
3. Wagstaff AJ and Perry CM. Topical imiquimod: a review of its use in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions. *Drugs* 2007; 67(15): 2187–2210.
4. Bubna AK. Imiquimod - its role in the treatment of cutaneous malignancies. *Indian J Pharmacol* 2015; 47(4): 354–359.

5. Stanley MA. Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. *Clin Exp Dermatol* 2002; 27(7): 571–577.
6. Navi D and Huntley A. Imiquimod 5 percent cream and the treatment of cutaneous malignancy. *Dermatol Online J* 2004; 10(1): 4.
7. Krishnasamy SR, Almazan TH, Suero-Abreu GA, et al. Successful treatment of cutaneous metastatic breast cancer with topical treatments that potentially synergize with systemic therapy: a case series. *JAAD Case Rep* 2018; 4(7): 711–715.
8. Dewan MZ, Vanpouille-Box C, Kawashima N, et al. Synergy of topical toll-like receptor 7 agonist with radiation and low-dose cyclophosphamide in a mouse model of cutaneous breast cancer. *Clin Cancer Res* 2012; 18(24): 6668–6678.
9. Adams S, Kozhaya L, Martiniuk F, et al. Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer. *Clin Cancer Res* 2012; 18(24): 6748–6757.
10. Salazar LG, Lu H, Reichow JL, et al. Topical imiquimod plus nab-paclitaxel for breast cancer cutaneous metastases: a phase 2 clinical trial. *JAMA Oncol* 2017; 3(7): 969–973.
11. Steinmann A, Funk JO, Schuler G, et al. Topical imiquimod treatment of a cutaneous melanomametastasis. *J Am Acad Dermatol* 2000; 43(3): 555–556.
12. Ray CM, Kluk M, Grin CM, et al. Successful treatment of malignant melanoma in situ with topical 5% imiquimod cream. *Int J Dermatol* 2005; 44(5): 428–434.
13. Rozenblit M, Hendrickx W, Heguy A, et al. Transcriptomic profiles conducive to immune-mediated tumor rejection in human breast cancer skin metastases treated with Imiquimod. *Sci Rep* 2019; 9(1): 8572.