Electrochemotherapy in the Treatment of Massive, Multisite Breast Cancer Metastasis to the Skin and Subcutaneous Tissue: A Case Report

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Established Facts

- The chest wall is a relatively common site for breast cancer recurrence after mastectomy, and between 10 and 15% of patients demonstrate regional recurrence in the area of the scar after mastectomy within 10 years of surgery.

Novel Insights

- Electrochemotherapy is an effective local therapy for patients with unresectable breast cancer recurrence or metastasis to the skin and subcutaneous tissue.
- Our case of breast cancer recurrence to the chest wall, which occurred in a 61-year-old woman, represents a spectacular regression of cutaneous metastases on the largest skin surface area published to date.

Keywords

Breast cancer · Chest wall recurrence ·
Electrochemotherapy · Bleomycin

Summary

Background: Chest wall recurrence (CWR) from breast cancer after mastectomy is a difficult to treat disease. Electrochemotherapy (ECT) provides a safe, efficient, and non-invasive locoregional treatment approach in this setting. **Case Report:** A 61-year-old woman presented with unresectable breast cancer recurrence to the skin and subcutaneous tissue for which numerous lines

of treatment were unsuccessful. Between February 2015 and May 2015, the patient underwent 3 courses of ECT after which a spectacular regression of the cutaneous metastatic foci was observed. After an overall observation period of 12 weeks, complete clinical remission was achieved. **Conclusion:** ECT can be proposed as an effective and safe locoregional therapy for breast cancer CWR and provides an alternative treatment modality to conventional therapies, especially in the case of multiple cutaneous and subcutaneous lesions.

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Introduction

Breast cancer is the most common cause of skin metastases in women [1–3]. The probability of their occurrence ranges from about 5% for the entire population to as much as 24% in the late stages of the disease [4, 5]. Although rarely life-threatening, skin metastases can have a major impact on a patient's quality of life, being the cause of pain, effusion, ulceration, infection, and psychological strain [6, 7].

Available methods of treatment, both local and systemic, often fail to provide adequate control of the disease. A particular challenge seems to be the treatment of those patients with extensive cutaneous metastases not eligible for resection, and in whom radiation therapy has already been applied and systemic therapy is ineffective or contraindicated.

We present the case of a patient treated with electrochemotherapy for massive, multisite breast cancer metastasis to the skin and subcutaneous tissue, in whom numerous earlier lines of treatment were unsuccessful.

Case Report

The patient was a 61-year-old woman suffering from obesity, hypertension, diabetes type 2, and nephrolithiasis.

In July 2009, she had been diagnosed with cancer of the right breast, stage IIIC (cT1 N3). An 8-mm tumor was present in the upper outer quadrant, and clinically suspicious lymph nodes were found in the armpit and supraclavicular region. The histopathological examination of a core needle biopsy revealed invasive ductal carcinoma (G3) and features of angioinvasion; the tumor was hormone receptor-positive (estrogen receptor (ER) 90%; progesterone receptor (PR) 80%) and HER2-negative. A fine needle aspiration biopsy was performed on the supraclavicular lymph node confirming metastasis (fig. 1).

In September 2009, after 3 cycles of neoadjuvant chemotherapy with adriamycin and docetaxel (AT), a modified radical mastectomy (Madden technique) with dermatoplasty (Y technique) was performed along with removal of the cervical lymph nodes.

In the postoperative histopathological examination, cancer foci were found in 13 of 14 collected axillary nodes and in 2 collected subclavian nodes. However, none of the 18 cervical nodes level II, III, and IV were occupied by tumor. The primary cancer site was not found (ypT0N3a).

After surgery, the patient received a further 3 cycles of AT chemotherapy, and in January 2010 she received adjuvant radiotherapy to the chest wall and regional lymph nodes, which was complicated by an episode of deep vein thrombosis in the right lower extremity with postthrombotic syndrome. Next, the patient qualified for hormonal therapy with letrozole which was started in April 2010. After radiotherapy, a considerable lymphedema of the right upper extremity occurred, which was treated with physiotherapy with varying success.

In January 2013, the patient was diagnosed with spread of cancer to the skin and subcutaneous tissue of the chest in the area of the mastectomy scar. Histopathological verification confirmed the presence of breast cancer foci of phenotype: ER 10%; PR < 1%; HER2 ambiguous, fluorescence in situ hybridization (FISH) negative.

From February to April 2013, the patient received 4 cycles of palliative chemotherapy with liposomal doxorubicin and cyclophosphamide. The treatment was terminated due to clinical progression of the skin lesions. An attempt to use hormonal therapy with exemestane also ended in a rapid growth of lesions, with progression to the skin of the left breast and surrounding area and occurrence of new foci in the skin of the abdomen. Within some lesions present in the skin folds around the breast, the patient developed shallow, oozing, painful ulcers. Moreover, lymphedema of the left upper extremity was diagnosed.

Fig. 1. Patient before treatment.

Fig. 2. Patient after treatment.

In August 2013, another line of palliative chemotherapy was applied according to the NX regimen (capecitabine 2,000 mg/m² orally days 1–14 and vinorelbine 60 mg/m² orally days 1 and 8 of a 3-week cycle). After 4 cycles of chemotherapy, a partial regression of the cutaneous metastases was achieved, and, consequently, a simple cosmetic mastectomy of the left breast could be performed in January 2014. At the same time, malignancy of the skin changes on the abdomen was histopathologically confirmed.

After surgery, the patient qualified for continuation of NX chemotherapy. She received an additional 5 cycles with disease stabilization until June 2014 when she was diagnosed with progression of skin lesions around the left-sided mastectomy scar.

In view of deteriorating hematological parameters indicating poor treatment tolerance with chemotherapy, an attempt was made to use palliative hormonal therapy with fulvestrant at a dose of 500 mg once a month. Transient disease stabilization was achieved, then progression of the skin metastases was observed with new skin lesions in the interscapular area and pain in the lower abdomen. In December 2014, hormonal therapy was completed, and palliative radiotherapy to the changes in the right-sided abdominal wall was performed (5 × 4 Gy). The patient then qualified for palliative chemotherapy with paclitaxel at a dose of 80 mg/m² once a week.

During the entire treatment period, none of the repeatedly performed imaging tests (ultrasound, X-ray, computed tomography, scintigraphy) revealed any metastases outside of the skin and subcutaneous tissue.

Then, between February 2015 and May 2015, the patient underwent 3 courses of electrochemotherapy. The treated areas of the body were the skin of the chest including the mastectomy scars on both sides up to the posterior axillary line, the skin of the upper, middle and lower abdomen on the right side, the skin of the upper abdomen on the left side, and the skin in the subscapular area on the right side. The total skin surface treated with electrochemotherapy measured approximately 1,500 cm². On the day before each treatment, a thorough physical examination was carried out and the planned treatment area was marked on the skin. The procedure was performed under general anesthesia with standard hemodynamic monitoring. The duration of the procedure was on average 45 min, including an average of 28 min of electrochemotherapy. In accordance with the ESOP guidelines, 8 min. before delivery of the first electric pulse the patient was given a chemotherapeutic agent: bleomycin at a dose of

15,000 IU/m² [8]. Electroporation was carried out in accordance with the instructions of the Cliniporator™ control system (IGEA, Carpi, MO, Italy) using hexagonal disposable needle electrodes. Hospitalization time was an average of 2 days. After surgery, the patient was monitored for the first 2 months every 2 weeks, and monthly thereafter.

In the treatment intervals, chemotherapy with paclitaxel was continued at a rhythm adjusted to the pace of the healing of the skin lesions and to the hematological tolerance. Due to a lack of clinical data on using electrotherapy simultaneously with paclitaxel and in view of potential conflicts due to the different mechanisms of action (anti-angiogenic activity of paclitaxel vs. need for adequate perfusion of bleomycin administered intravenously into the tumor), a principle was adopted of a minimum 10-day interval separating both treatments. Electrochemotherapy was well tolerated [9].

A spectacular regression of the cutaneous metastatic foci was observed: after 6 weeks of observation, partial remission was seen, and after 12 weeks, complete clinical remission was achieved along with reduced pain and a decreased demand for analgesics, gradual healing of pre-existing ulcers, and a subjective improvement of the patient's well-being (fig. 2).

Discussion

Electrochemotherapy is a relatively new local cancer treatment, especially for lesions not responding to other types of treatment [10, 11]. It is based on the phenomenon of reversible electroporation, i.e. a temporary increase in cell membrane permeability due to the interaction of an adequately modulated electric field which increases the intracellular concentration and, consequently, activity of cytostatic drugs administered locally or systemically. The most suitable cytostatics are bleomycin and cisplatin. Bleomycin may be administered intravenously or into the tumor, cisplatin into the tumor only [12]. Bleomycin demonstrates the highest increase in cytotoxic activity under conditions of electroporation [13]. Since the first publication in the 1990s [12, 13], effectiveness of electrochemotherapy has been demonstrated in the palliative treatment of many cancers: primary and secondary tumors of the skin, head and neck tumors, superficial sarcomas, and metastases to various solid organs or bones [5, 10, 11]. Marty et al. [8], in a study of ESOPE guidelines in a group of 14 patients with breast

cancer metastasized to the skin, obtained 90% complete responses and 5% partial responses to the treatment. Recently, the use of electrochemotherapy in radical treatment has also been explored (e.g. as part of neoadjuvant procedures in inoperable breast cancer) [14]. Furthermore, studies are being conducted its use for the transport of other drugs into cells, such as immunomodulators or vectors used in gene therapy [15, 16].

Although the factors influencing the effectiveness and toxicity of this method are fairly well known (types of electrodes, characteristics of the current, cytostatic dose, and interval between administration and treatment), there is a lack of sufficient data considering its optimal combination with other treatments.

Conclusion

Electrochemotherapy is a method with documented efficacy in the palliative treatment of patients with metastases to the skin or with unresectable recurrence of breast cancer. The local effectiveness of this method allows for significant improvement of the quality of life of patients in whom local tumor spread has resulted in the formation of ulcerated, bleeding, exophytic tumors, and who at the same time are not eligible for resection or fail to respond to systemic treatment. Thanks to its simplicity, while targeting exclusively the local growth of tumors in the skin, this method can be used repeatedly and also in patients with a history of internal diseases. Currently, electrochemotherapy is used in 80 European centers based on established standards [8]. However, there are no published studies on large groups of patients which would allow to firmly establish the place of this therapy in combination treatments used in patients with stage IV cancer.

Disclosure Statement

The authors have no conflict of interest to declare.

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