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# Xeloda Oral, Trastuzumab, and Pertuzumab Combined Drug Therapy Reduced Cervical Lymphadenopathy and Dermal Involvement in Patient With Recurrent Breast Cancer: Case Report

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**Abstract**

We report the case of a 42-year-old woman who was diagnosed with breast cancer that recurred 3 years later, with supraclavicular lymphadenopathy and dermal involvement. The main drug used in the therapy was trastuzumab; however, the association of this drug with docetaxel was not able to decrease or cease the effect of the inflammatory BCA component with erythema and thickening of the skin as well as the supraclavicular lymphadenopathy previously diagnosed. Thus, a combined therapy was required. The patient was started on 6 cycles (1 per month) of trastuzumab subcutaneous 600 mg, pertuzumab intravenous 840 mg (as an attack dose, later on 420 mg), and xeloda oral 1000 mg. As a result, the patient showed a significant improvement in erythema and thickening of the skin in the neck and the right part of her trunk, besides decrease in supraclavicular lymphadenopathy. After 6 cycles, her skin was almost restored. Intravenous trastuzumab can be an effective single agent; however, its association with other chemotherapies—such as pertuzumab—can present a synergic effect, which can increase the survival expectations of metastatic HER2+ patients. Additionally, as reported in the literature, the use of xeloda plays a key role in restoring the skin health of patients with breast cancer presenting with skin metastasis. Our findings suggest that trastuzumab, pertuzumab, and xeloda combined therapy, following the schedule and posology handled in this study, can be a good treatment for recurrent HER2+ breast cancer with signs of supraclavicular lymphadenopathy and severe inflammatory BCA component with erythema and thickening of the skin.

**Keywords**

breast cancer, supraclavicular lymphadenopathy, HER2-positive, combined chemotherapy, inflammatory BCA component

## Introduction

Breast cancer is the most common cancer among women, with 2.1 million cases reported each year. In Chile, breast cancer is also the main health concern for women, since nearly 4000 cases are diagnosed each year, reaching 12.8% of the causes of death in the female population.[1,2]

The greatest concern of patients with breast cancer is the possibility of metastasis: it can be found in any organ including in the skin and neck. Although rare, supraclavicular metastasis—which happens when distant metastases of breast carcinomas reach the neck—also occurs in breast cancer patients and not only in head and neck malignances.[3,4] Additionally, it is known that breast cancer can evolve to the inflammatory form (known as inflammatory breast cancer), affecting the derma. This type of breast cancer is uncommon, but aggressive, invasive, and generally leads to metastasis earlier.[5] Generally, when breast cancer spreads to other organs there are less chances of healing. Moreover, the standard and systematic therapy can be difficult in some cases; for example, when the patient has lymph node involvement, a combined therapy is required.[6]

Many chemotherapies are being used on patients with recurrent breast cancer, HER2-positive, with metastatic signs, erythema, thickening of the skin, and supraclavicular lymphadenopathy. Trastuzumab, a recombinant human monoclonal IgG1 antibody that targets the epidermal growth factor 2

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(HER2) protein, is used for the treatment of breast cancer HER2-positive.[7] As a single agent, it is a potent adjuvant against breast cancer; however, a synergic effect can be observed when this chemotherapy is associated with other drugs.[8] A combined therapy of trastuzumab and pertuzumab plus docetaxel is a first-line treatment in the metastatic setting.[7,9]

It is known, however, that docetaxel is a cytotoxic agent that often presents several acute and long-term secondary effects. Generally, several acute secondary effects such as fever, dyspnea, hypoxia, urticaria, and cardiorespiratory arrest can occur within minutes or hours after drug administration.[10] A good substitute to docetaxel used to treat breast cancer metastasis with cutaneous involvement is xeloda, generally associated with other anticancer agents. Sideras and colleagues[11] reported the case of an 82-year-old female with breast cancer and cutaneous metastasis presenting several nodules over the breast and chest wall. Xeloda was administered in 700 mg/m$^2$ doses, which were well tolerated; and after only 2 cycles, the patient presented significant improvement in her inflammatory breast condition. Additionally, the authors related no progression of the disease after 10 cycles of treatment.[11]

In this sense, we came across the study of a case of recurrent advanced stage breast cancer, in which cervical skin ulcer and inflammatory BCA component with erythema and thickening of the skin were detected after a 42-year-old woman consulted an oncologist for right supraclavicular lymphadenopathy appearance during breast cancer follow-up care. A combined therapy using xeloda oral, trastuzumab, and pertuzumab was chosen for her treatment, which resulted in a significant response with decreasing of supraclavicular skin ulcer as well as decreasing of the inflammatory process in the breast skin.

## Clinical Case

A 42-year-old woman without other relevant medical history was diagnosed with breast cancer in 2013, when she was 36 years old. For the diagnosis of this breast cancer case, macroscopic and microscopic evaluation in biopsies of right mammary gland and axillary tail were performed. A core biopsy of mammary gland tissue measuring around 6.5 × 4.5 × 2.3 cm and with 41 g of weight was evaluated. At the macroscopic level, a fibrous area measuring 1 × 1 × 1 cm in upper portion of this biopsy was identified. The remaining evaluated fragment of breast tissue presented adipose appearance. The core biopsy of the axillary tail, which was represented by an irregular fragment of fibro-fatty tissue measuring 8 × 6 × 3.5 cm, showed lymph node affection. Nine lymph nodes were dissected and 2 of them presented metastatic appearance. Concerning the microscopy analysis, the core biopsy of mammary gland tissue presented a chronic inflammatory process with lobular involution (atrophy) as well as fatty involution and fibrosis. Additionally, the presence of a fibrous area with evident process of tumorigenesis was identified. Finally, a mild mammary duct ectasia and regular lymphocytic infiltration was identified. In the axillary tail, the 2 affected lymph nodes showed an intranodal and perinodal metastatic tumor (1.1 cm of diameter). Other 7 evaluated lymph nodes presented chronic lymphadenitis with dystrophic calcifications in 2 of them. According to these findings, the tumor was characterized as T1N2M0.

Thirty months after the diagnosis, she presented a right supraclavicular nodule, which resulted, through core biopsy, in a poorly differentiated carcinoma, negative for hormonal receptors HER2-positive, with a Ki-67 index around 30%. Furthermore, she presented severe inflammatory BCA component with erythema and thickening of the skin over the right breast and superior portion of trunk.

The patient's therapy regarding medicine dosage and treatment schedule is shown in Table 1.

## Results

During the phase of diagnosis, the patient received neoadjuvant chemotherapy involving fluorouracil, adriamycin, and cytoxan (6FAC) for a period of 6 months until she was submitted to partial mastectomy and axillary dissection. After this procedure, a new phase of treatment started including adjuvant radiotherapy (2 grays daily, 25 doses) for almost 2 months, as well as trastuzumab therapy (see Table 1). She was followed-up for the next 9 months, a period during which she remained asymptomatic.

However, 30 months after the diagnosis and the start of the treatment, she presented a right supraclavicular nodule and dermal involvement. Due to these conditions, a treatment with docetaxel and trastuzumab was started and administrated for 2 months, but it had to be suspended after the first 2 cycles of docetaxel due to a strong allergic reaction of the patient. During docetaxel administration, the patient presented neutropenia grade 1 and an acute allergic reaction consisting of bronchospasm, headache, and dyspnea. However, the therapy with trastuzumab continued and the trastuzumab chemotherapy in metastatic modality was used to substitute docetaxel, due to the appearance of right supraclavicular nodule (see Table 1 for medicine doses).

Despite this treatment, the progression of right supraclavicular lymphadenopathy remained. The radiotherapy team evaluated the case and decided to reject the radiation treatment due to the extensive injuries in the neck area. Even while receiving the therapy, the patient presented severe inflammatory BCA component with erythema and thickening of the skin (covering up to one third of the neck) and right clavicular and scapula associated with cervical lymphadenopathy ranging from stage I to IV. Due the advanced status of lymphadenopathy and evident inflammatory process in her derma, a treatment with paclitaxel was offered, but it was rejected by the patient due to the previous allergic reaction to docetaxel treatment.

**Table 1.** Patient's Chemotherapy Schedule.

| Antitumor agent | Dosage | Clinical event |
|---|---|---|
| 6FAC | 6-Fluororacil 900 mg<br>Adriamycin 90 mg<br>Cytoxan 900 mg | T1N2M0 |
| Radiotherapy | 2 grays/25 dose | Post-surgery (partial mastectomy and axillary dissection) |
| Trastuzumab | 600 mg subcutaneous | Chemotherapy post radiotherapy and surgery |
| Docetaxel<br>Trastuzumab | Docetaxel 112 mg<br>Trastuzumab 600 mg | Breast cancer recurrence with right supraclavicular nodule. After 2 cycles were suspended due strong reaction in the patient. |
| Traztuzumab<br>Metastatic modality | Trastuzumab 600 mg | Right supraclavicular lymphadenopathy remained, impossibility to use radiotherapy |
| Trastuzumab<br>Pertuzumab<br>Xeloda | Trastuzumab subcutaneous 600 mg (28 cycles)<br>Xeloda oral 1000 mg (6 cycles)<br>Pertuzumab endovenous 840 mg (attack dose) and 420 mg (6 cycles) | Treatment of severe breast dermal involvement and visible right supraclavicular lymphadenopathy |

To understand the development and severity of the evident lymphadenopathy cervical and dermal involvement in the patient and evaluate the lesions in her skin, a new computed tomography scan was requested. This first analysis evaluated skin, muscle, and right lymph node involvement and showed that there was no presence of the disease in those areas, even though the neck and cervical injuries were evident. Considering the unsatisfactory results of the previous treatments, it was decided to start a new therapy combining xeloda oral, trastuzumab, and pertuzumab. During the initial 6 cycles of treatment, the patient showed a clear clinical improvement, with an evident decrease in the progress of cutaneous metastasis.

The process of recovery of the skin and cervical area during the treatment is shown in Figure 1. All the mentioned treatments were not able to cease or decrease the dermal involvement until the patient started the combined therapy. Figure 1A-C shows the patient's supraclavicular and neck region before the treatment. Figure 1D-F shows the patient's evolution after 6 cycles of trastuzumab, pertuzumab, and xeloda.

## Discussion

Patients with HER2-positive breast cancer generally present with poor prognosis and high recurrence rates. Also, it is known that drugs such as trastuzumab and pertuzumab—human monoclonal antibodies that act against the HER2 protein—are extensively used in the treatment of breast carcinomas expressing this protein.[8,12] The clinical features of breast cancer presented in this case study, which are the profile HER2-positive, hormonal receptor negative, and metastatic cancer, have led to the use of trastuzumab as the main chemotherapy treatment. Even though intravenous trastuzumab can be an effective single agent, one disadvantage in the use of trastuzumab is the primary or acquired resistance observed in several patients, which can compromise its therapeutic effectiveness.[8] Rates of resistance to trastuzumab observed in patients with breast cancer can range from 66% to 88%.[13-17]

Resistance to trastuzumab could be expected in this patient since the treatment with trastuzumab metastatic modality, as a single agent, did not present any response concerning the control of her breast dermal involvement and cervical skin ulcer. Given such conditions, the combined therapy is recommended. Due to trastuzumab and pertuzumab blockage of the same protein through different ways, in this study these drugs were combined to treat the patient with breast cancer HER2-positive. Such combination can provide a more effective blockage of the HER2 signaling pathways, resulting in a better antitumor strategy, which can potentiate the antitumor activity[18] as well as inhibit the survival of breast cancer cells.[19,20] For the treatment of patients with breast cancer recurrence and dermal involvement, a combined therapy is also required. Generally, patients who received pertuzumab, trastuzumab, and docetaxel showed significant response to the treatment and a higher increase in the progression-free survival and overall survival than the group that only received trastuzumab, docetaxel, and placebo.[9] However, many patients presented adverse events as classical hypersensitivity or acute side effects during docetaxel administration.[9] The patient studied presented acute side effects as neutropenia grade 1 and acute allergic reaction consisting of bronchospasm, headache, and dyspnea. For this, another antitumor agent to treat her erythema and thickening of the skin was necessary. At this point, the treatment applied showed no improvement in the dermal involvement of breast skin and decreasing of the supraclavicular lymphadenopathy.

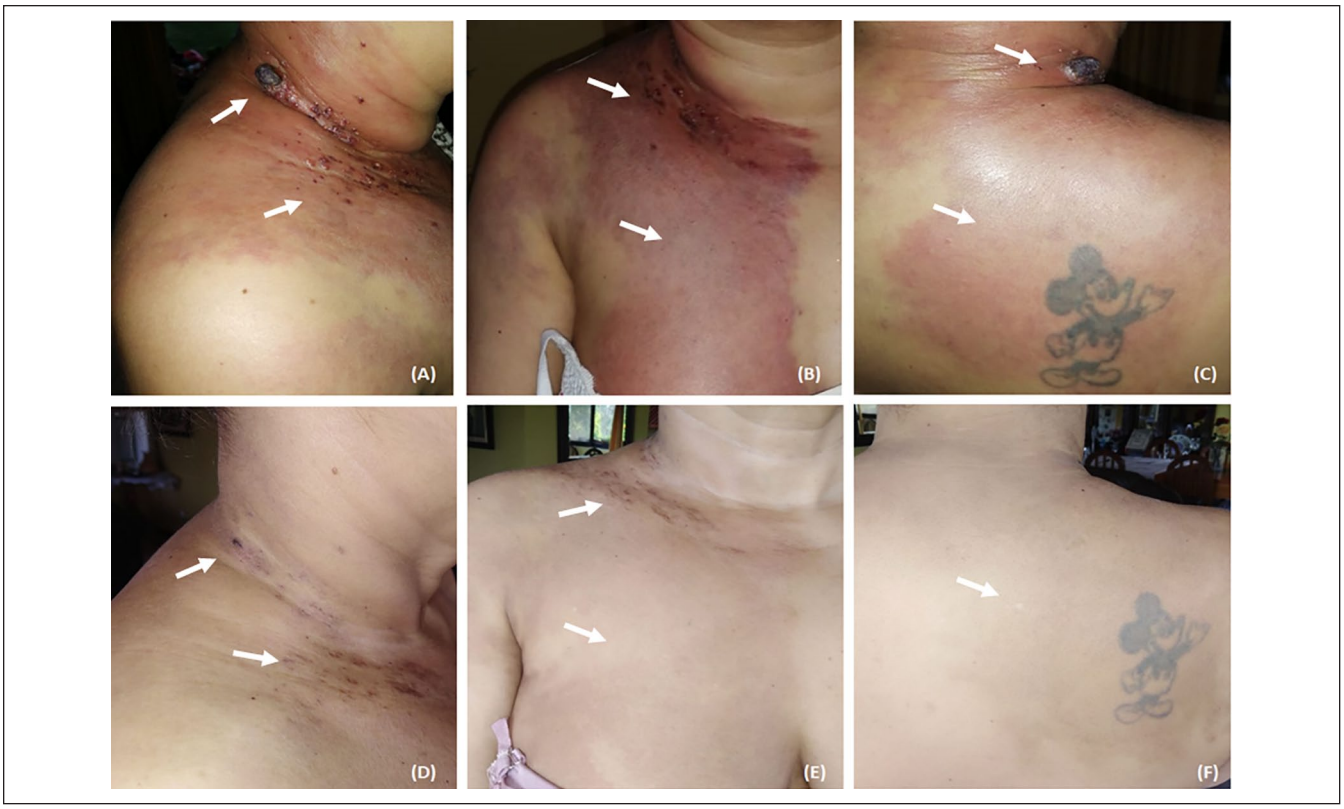


**Figure 1.** Patient's treatment history. (A) Evident cervical skin ulcer; (B) and (C) dermal involvement in the neck and right breast, photos before chemotherapy and herceptin plus pertuzumab treatment. (D) Improvement of skin ulcer; (E) and (F) dermal involvement improvement, photos after 6 cycles of xeloda oral, trastuzumab, and pertuzumab drugs treatment. The white arrows show the affected areas in study.

Thus, xeloda was added to the treatment schedule since neither the therapy with trastuzumab and docetaxel in the indicated doses (Table 1) nor the trastuzumab metastatic modality were able to decrease or cease the dermal involvement of the patient's neck and the supraclavicular lymphadenopathy. In this sense, it is important to mention that Tsuyuki and colleagues[21] investigated 30 patients with advanced metastatic breast cancer and reported that xeloda is an effective drug to treat soft tissue lesions, such as primary tumor and metastasis of skin and lymph nodes. In addition, they stated that the effective response of xeloda was significantly higher in soft tissues than in other types of metastasis (lung, liver, and bone). As a result, they suggested that the use of this drug as the upfront line for soft tissue metastatic cases can contribute to the overall survival.[21] Breast cancer with dermal involvement can be treated with xeloda. Two women aged 61 and 82 years presented significant improvement in their erythema of the skin after 2 cycles of xeloda and did not show progression for more than 10 months.[11]

The patient studied here presented the same pattern that the one described in literature during her treatment with the combined therapy using trastuzumab, pertuzumab, and xeloda. She soon presented a substantial improvement in her lesions in the neck and skin as well as a decrease in the lymphadenopathy; after 6 cycles of combined therapy, her skin was almost restored (see Figure 1 D-F). Additionally, a computed tomography scan performed after the treatment only showed signs of regional subcutaneous cell tissue edema. Normal blood count and normal cardiac analysis were also obtained.

The effects of trastuzumab and pertuzumab use on dermal involvement of the patient were not visible. However, it can be expected that this combined therapy helped avoid the appearance of new tumors in other areas and to maintain the patient without evident cancer progression. Additionally, it is possible that the patient had acquired resistance to the use of trastuzumab as a single agent, but when the treatment schedule was changed to a combination of trastuzumab and pertuzumab, the observed synergic activity potentiated the antitumor action of these medicines. Finally, in this study, xeloda plays a key role in the treatment of severe inflammatory BCA component with erythema, thickening of the skin, and supraclavicular lymphadenopathy by restoring the skin health,[20] turning this combined treatment into an effective strategy to treat patients who present with recurrent breast cancer and show signs of cutaneous metastasis and supraclavicular lymphadenopathy.

## Conclusions

A 42-year-old woman diagnosed with HER2-positive breast cancer presented recurrence in her tumor as well as supraclavicular lymphadenopathy and severe inflammatory BCA component with erythema and thickening of the skin. Since the lesions reached a higher level, the treatment with neoadjuvant radiotherapy was not viable. In addition, the patient did not respond satisfactorily to the treatment that consisted in the use of trastuzumab with dectaxel or trastuzumab metastatic modality, complicating her therapy. Given these issues, it was decided to start a combined therapy with trastuzumab, pertuzumab, and xeloda, which proved to be an effective combination showing improvements after 3 cycles, restoring the skin health and decreasing almost completely the lymphadenopathy detected after 6 cycles.

Even though the effects of the medicines in this patient are still not perfectly clear, our results suggest that the combined therapy with trastuzumab, pertuzumab, and xeloda, following the schedule and posology described here, can be a good treatment for recurrent HER2-positive breast cancer with supraclavicular lymphadenopathy and severe dermal involvement. This conclusion was reached not only because the synergic action between trastuzumab and pertuzumab increased the antitumor activity in both drugs but also because the action of xeloda in soft tissue with metastasis restored the skin heath.

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### Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

### Informed Consent

The patient provided written consent for publishing this work.

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