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Case report

Breast cancer local recurrence under the form of inflammatory carcinoma, treated with concurrent radiation and chemotherapy, a case report

Isabel Reis[a,*], *Helena Pereira*[a], *Isabel Azevedo*[a], *João Conde*[a], *Isabel Bravo*[b], *Rogéria Craveiro*[b], *Deolinda Pereira*[c]

[a] *Radiation Oncology Department, Instituto Português de Oncologia Francisco Gentil do Porto, E.P.E., Porto, Portugal*
[b] *Radiobiology Lab, Instituto Português de Oncologia Francisco Gentil do Porto, E.P.E., Porto, Portugal*
[c] *Oncology Department, Instituto Português de Oncologia Francisco Gentil do Porto, E.P.E., Porto, Portugal*

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ABSTRACT

The authors present a case report of a patient with breast cancer diagnosed in 2005, treated with conservative surgery, adjuvant chemotherapy and radiotherapy, followed by hormonal therapy until 2010, who relapsed under the form of inflammatory breast cancer in 2011. After tumor progression detected during primary systemic therapy, a concurrent radiation and radiosensitizing chemotherapy were proposed. There was a significant clinical response to this treatment, enabling curative chance with total mastectomy. The histological examination of the breast and regional lymph nodes revealed a complete response, since there was no evidence of residual tumor.

There are few reports concerning concurrent radiotherapy and chemotherapy in locally advanced breast cancer, but it could be a suitable "loco regional rescue therapy" to further reduce tumor progression and allow curative surgery. Study of this treatment strategy in randomized clinical trials is warranted.

1. Background

Inflammatory breast cancer (IBC) is a rare subgroup of locally advanced breast cancer (LABC) that presents particular management challenges. This biologically aggressive disease, clinically diagnosed, is more frequently seen in women that have never had breast cancer, but it can also develop in a breast that contains a known tumor or that has been previously treated.[1]

The prognosis of patients with LABC has improved over the last 2 decades, with the recognition of the efficacy of a multimodality approach. Advances in neoadjuvant chemotherapy (CT) in this setting include not only earlier treatment of sub-clinical distant micrometastases and primary tumor downstaging, but also the possibility of *in vivo* assessment of tumor response. Thus, it is not only rational, but also current practice, to apply this approach in unresectable LABC.[2] According to current guidelines, preoperative CT consisting of anthracycline based regimens with or without taxane are

* *Corresponding author at*: Instituto Português de Oncologia Francisco Gentil do Porto, E.P.E. Rua Doutor António Bernardino de Almeida, 4200 Porto, Portugal. Tel.: +351 963844197.
E-mail address: isabelreis_85@hotmail.com (I. Reis).

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now recommended. Her-2-positive patients should receive an initial CT program incorporating preoperative trastuzumab. For operable tumors after CT, this treatment should be followed by local therapy consisting of total mastectomy or lumpectomy, with a level I/II axillary lymph node dissection, when necessary. Both groups are considered to have sufficient risk of local recurrence to warrant the use of chest wall (or breast) and supraclavicular node irradiation. Adjuvant therapy may involve completion of planned CT regimen course if not completed preoperatively, followed by endocrine therapy in patients with hormone receptor-positive disease. However, only 10–20% of patients achieve a complete clinical response, and 50–60%, partial response to induction CT.[3–5]

For patients whose tumors remain inoperable despite induction systemic therapy, the optimal management strategy has not been established. Preoperative radiotherapy (RT) has been used, but few data are available regarding this approach. Therefore, this treatment modality has not been widely used in patients with LABC.

Radiosensitizers are chemical agents that can modify tumor response to RT. This citotoxic enhancement explains the ability of chemotherapy to induce lethal effects in tumor cells and interfere in their capability of repairing DNA damage, when administered together with radiation.[6] The benefit provided by RCT is greater than it would be expected from the mere additivity of the independent effects of each modality.[6]

In fact, concurrent CT and RT have successfully improved both local control and overall survival (OS) in other cancers such as naso and oropharynx,[7] oesophagus,[8] cervix[9] and anal cancer.[10] Based on this experience, it is reasonable to exploit the synergism of this two therapeutic modalities in LABC, since this approach could allow more patients to proceed surgery and improve local control.

2. Case report

A 46-year-old premenopausal woman presented with a complaint of a breast mass, located in the right upper outer quadrant (UOQ). She has been taking oral contraceptives over the past 15 years. Menarche occurred at the age of 14, and her first pregnancy at 30 (Gravida 2 Para 2 Abortion 0). Family history was negative for both breast and ovarian cancers.

On physical examination, there was a palpable, non-tender mass measuring about 2.0 cm in the UOQ of the right breast. There was no mammilar discharge, but it was possible to identify skin retraction around the mass. Peripheral lymph nodes were not palpable. The rest of the examination was within normal limits.

Mammography showed a high-density mass without calcification and an indistinct margin in the UOQ of the right breast. Ultrasonography revealed a 1.3 cm sized hipoecogenic mass in the same location. No adenopathies were identified in the imagiologic study.

The fine needle aspiration biopsy revealed carcinoma. The clinical stage was determined to be cT1cN0M0 according to the AJCC staging system.

The patient had undergone wide excision with negative margins (>2 mm) and sentinel lymph node biopsy in October 2006. The histological diagnosis was Invasive Ductal Carcinoma (IDCA), grade III, measuring 2.2 cm plus Extensive Intraductal Component (EIC), high grade, with micro invasive foci. Three sentinel lymph nodes were excised, none with metastasis. Immunohistochemical (IHC) examination showed the presence of both estrogen receptors (ER) and progesterone receptors (PgR) in 10% of tumor cells and showed strong membrane staining of HER-2 (3+ score). The pathologic stage was determined to be pT2N0snM0 (Stage IIA).

The patient received postoperative adjuvant CT consisting of 6 cycles of 5-fluoruracil, adriamicine and cyclophosphamide, between November 2006 and February 2007 (total dose of 504 mg of each agent), in combination with the humanized monoclonal antibody, trastuzumab (initially 8 mg/kg followed by 6 mg/kg every 3 weeks), which was maintained for 1 year.

She also received postoperative adjuvant RT, with total dose of 50 Gy at 2 Gy/day × 25 fractions to the whole right breast, with tangencial fields and 4 MV energy. The boost was administered with Intersticial Brachitherapy: 20 Gy, 85% of basal dose to tumor loci, with Iridium-192, at pulsed dose rate. RT was completed on April 2007.

To complete the treatment, the patient received hormonal therapy (HT), with tamoxifen, from April 2007 to April 2011. She also received goserelyn from February 2008 to March 2010.

The patient was kept in follow-up, and there was no evidence of loco-regional or distant recurrence for more than 4 years.

On April 2011, an erythematous skin lesion was identified in the right breast, involving both the superior quadrants and the inferior inner quadrant, occupying a total area of 10 cm × 14 cm. This was an unresectable lesion, associated with inflammatory signs, namely erythema, pain, warmth and pitted appearance (*peau d'orange*) of the right breast. The rest of the physical examination was within the normal limits.

Mammography showed augmented skin thickness, without an individualized mass, a typical feature of IBC.

The histological examination of the core biopsy revealed ICDA with involvement of the dermis, and vascular invasion. ER and PgR were negative, and staining for Her-2 scored 2+.

The patient underwent adequate staging examination which did not reveal distant disease.

In the presence of this local recurrence, under the form of IBC, and given its unresectability, the patient received primary systemic therapy, consisting of docetaxel and carboplatin plus trastuzumab starting on April 2011. However, in August 2011, tumor progression was detected after 6 cycles of CT, and treatment was suspended. Posteriorly, it was decided to treat the patient with concurrent RT and CT. RT was delivered to the right breast, axilla and supra-clavicular fossa with the Rapid Arc technique, with total dose of 50 Gy at 2 Gy/day × 25 fractions, and 6 MV Energy. For the last 15 fractions, radiation was delivered using "bolus", a tissue equivalent material to ensure that full radiation dose was reaching the skin. Concomitantly, the patient received 5 cycles of docetaxel (35 mg/m^2, weekly). No severe adverse event above grade 3 skin toxicity was seen.

A significant clinical response to concurrent RT and CT was detected, and the lesion became operable. The patient underwent total right mastectomy with immediate reconstruction in December 2011.

Histological examination of the operative specimen did not show any residual carcinoma. The patient continued treatment with trastuzumab and today remains without evidence of loco-regional or distant recurrence.

3. Discussion

The use of neoadjuvant CT has become a standard of care for the management of LABC, including IBC. This treatment course enhances the possibility of surgery.[7,11,12] Nevertheless, it is now recognized that a proportion of breast cancers may be resistant or develop resistance to the chemotherapeutic agents initially used for their treatment.[13] This group of patients will never respond to treatment, with poor loco-regional control, impossible surgical resection, increased risk of distant metastases and bad quality of life. Approximately 30–40% of patients who achieve clinical response enabling surgical resection develop loco-regional relapse. Additionally, even though tumor progression under neoadjuvant CT is uncommon, it is clearly associated with a dismal prognosis.[14–16]

Treatment options for loco-regional recurrences are limited. CT might not be effective in previously irradiated tissue, because a decreased perfusion can be expected due to radiation-induced fibrosis.[17] This factor might have contributed to the absence of response to neoadjuvant CT verified in our patient, who has shown tumor progression during this treatment. Therefore, concurrent RT and CT were proposed. There are few reports concerning this strategy in LABC, but it could be a suitable "loco regional rescue therapy" to further reduce tumor progression and allow curative surgery, while maintaining systemic therapy. There are several potential advantages of this combination in the treatment of breast cancer, including earlier RT treatment, shorter duration of therapy, and synergistic activity between CT and RT, with improved efficacy.[18,19]

Retreatment with a second course of RT to the breast is to be used with caution as increased toxicity of skin and subcutaneous tissue is feared. Nevertheless, in recent years, several investigators reported on reirradiation. Data on more than 300 patients reirradiated for recurrent breast cancer, either alone or in combination with CT, endocrine treatment and/or hyperthermia, have so far been published. According to these studies, reirradiation is feasible and safe, at least within the first five years after treatment, with low to modest side effects offering a second curative chance.[20]

The published studies using concurrent RT and CT show pathologic complete response rates of ~35%.[21–23] In two consecutive phase I/II trials, 33 patients with unresectable LABC, including IBC or locally recurrent disease were treated with concurrent CT-RT. CT consisted of either continuous infusion or bolus paclitaxel with or without vinorrelbine, using a novel week on/week off (WO/WO) treatment schedule. This report demonstrated that concomitant paclitaxel-based CT and high-dose RT followed by mastectomy is an aggressive, but well tolerated treatment strategy. To the best of our knowledge, the pathologic response rate of 47% for initially unresectable Stage IIIB/C breast cancer seen in this study represents the highest pathologic response rate reported in the literature.[19]

Other combinations have been assessed in LABC deemed inoperable at diagnosis or considered refractory to neoadjuvant CT. The safety of combining vinorelbine/5FU and RT has already been evaluated and validated in a phase II trial.[24] These authors found three pathologic complete response-associated factors: histological grade 3; absence of hormonal receptors, and high mitotic index.[24] Here, all patients have been pretreated with anthracycline or taxane based pre-operative CT. This treatment could be expected to increase toxicity as a result of the synergistic effect of cell damage and apoptosis. However, in such a setting, "rescue" RT-CT was well tolerated with grade 2 skin toxicity as the most severe acute side effect.

Radiation pneumonitis has been a relatively rare problem of adjuvant therapy. Concurrent CT has been associated with higher rates of this complication. Other potentiating factors include addition of nodal irradiation, the extent of lung exposure to radiation, and underlying lung disease.[18] A retrospective analysis at the Massachusetts General Hospital evaluated the risk of pneumonitis in women who received adriamycin and cyclophosphamide with or without subsequent paclitaxel, with concurrent or sequential RT. Forty-one women were identified who had received adjuvant RT and paclitaxel, roughly half of whom received concurrent, and half sequential treatment. Paclitaxel was associated with a 15% risk of pneumonitis, compared with 1% risk in historical experience among women not treated with paclitaxel.[25] These results were not verified in other recent studies. Investigators from the University of Washington reported on a retrospective study of 44 women who had received either paclitaxel or docetaxel with concurrent radiation. There was no reported radiation pneumonitis in this study.[26] A prospective study from California reported on 24 patients treated with AC followed by paclitaxel with concurrent RT, and no pneumonitis was encountered.[27] Formenti and colleagues reported a trial of 44 T3-4N0-3 breast cancer patients treated with neoadjuvant RT (45–50 Gy) with concomitant twice-weekly paclitaxel (30 mg/m^2). A 16% pathological response rate was achieved with no cases of radiation pneumonitis.[28]

Our patient, treated with docetaxel and concurrent RT exhibited a very acceptable profile of toxicity: no radiation pneumonitis was detected, and no more than grade 3 skin toxicity was noted.

In conclusion, treatment of LABC, and particularly IBC, requires a coordinated multidisciplinary approach that should be individualized according to the tumor features and response to primary treatment. Although the optimal treatment to this disease remains uncertain, "rescue" taxane based CT and RT seems active, safe, and feasible as "secondary-line" neoadjuvant treatment for LABC that are refractory to standard anthracycline and taxane based neoadjuvant CT. The results found in a series of randomized clinical trials concerning this strategy support the study of this treatment strategy in randomized clinical trials, so this approach should be considered as part of loco-regional therapy for aggressive breast cancer.

Conflict of interest

None declared.

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