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Multidisciplinary and Tailored Treatment of LABC in Progression during NAC: Case Report

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Abstract: Locally Advanced Breast Cancer (LABC) is a complex disease that requires a multidisciplinary approach. Neoadjuvant Chemotherapy (NAC) is usually performed in order to achieve loco-regional radical resection; although its importance in the multidisciplinary approach to LABC is well recognised, a small number of patients show Progressive Disease (PD). No standard Salvage Treatment (ST) has been defined and different strategies can be adopted, such as second line systemic therapies, radiation therapy, and surgery. Herein a case of LABC in PD during NAC is reported with a literature review, with the aim of highlighting the importance of a tailored multidisciplinary treatment in each patient.

Keywords: Locally Advanced Breast Cancer (LABC); Progressive Disease (PD); Salvage Treatment (ST)

1. Introduction

Locally Advanced Breast Cancer (LABC) is an extensive breast cancer, without distant metastases, which may be resectable or unresectable; as compared to early breast cancer, it bears a worse prognosis due to unfavourable biological factors and the wider extent of loco-regional disease; hence, a multidisciplinary approach is essential for the management of this challenging disease. Herein is reported the clinical history of a 55-year-old post-menopausal woman with LABC who developed local Progressive Disease (PD) during Neoadjuvant Chemotherapy (NAC). She has been treated at San Martino Hospital in Genoa, in our Breast Unit.

2. Case presentation

The Patient detected a lump into the upper outer quadrant of the right breast in September 2021 and she was visited at another hospital. Clinically, she had palpable tumor into the right upper quadrant with skin redness; moreover, multiple lymph nodes were detectable into the homolateral axilla, the largest being about 15 mm. Mammography and breast Ultrasound (US) showed a suspicious neoplasm of 37 x 17 mm and the needle-biopsy demonstrated a high grade (G3) ductal invasive breast cancer, estrogen receptor (ER) positive (40%), progesterone receptor (PgR) negative, Ki67 = 40%, c-erb-2 protein positive (3+). Bone scintigraphy and total-body Computed Tomography (CT) scan were both negative for distant metastases. After Disease Multidisciplinary Team (DMT) evaluation, NAC was given including 4 cycles of Epirubicin-Cyclophosphamide (EC) followed by Trastuzumab and Paclitaxel for 12 weeks. The genetic assessment for BRCA-1 and BRCA-2 mutation was negative.

After 4 cycles of EC, breast US showed stable disease; moreover, although the previous clinically positive axillary lymph node of about 15 mm was no longer visible, a new axillary lymph node 5 mm in diameter was highlighted, while the remaining lymph nodes had a reactive appearance. After 6 cycles of NAC, a slight dimensional reduction of the breast lump (27 x 10 mm *vs* 37x17 mm) was observed at breast US, and the pathologic lymph nodes into the axilla were no longer detectable; therefore, the Patient continued the ongoing NAC regimen.

After five months of NAC, breast Magnetic Resonance (MR) showed minimal partial response of the breast lesion (25 x 10 mm in diameter) with negative axilla. However, skin redness and retraction had increased, with worsening ulceration (Figure 1). A second US-guided biopsy was then suggested, and G3, ER-negative, PgR negative, *Ki67* = 75%, c-erb-2 positive (3+) invasive ductal carcinoma was confirmed. After a new DMT discussion, breast disease was deemed unresectable, and Trastuzumab Deruxtecan in the expanded access programme (EAP) was started. However, after 4 cycles, due to unsatisfactory local control of disease, Radiation Therapy (RT) of the breast with concurrent chemotherapy (Trastuzumab Deruxtecan, Tucatinib and Capecitabine) were given. Bone scintigraphy was always negative but a pathologic lymph node at the level of the right pulmonary hilum was detected by total-body CT scan.

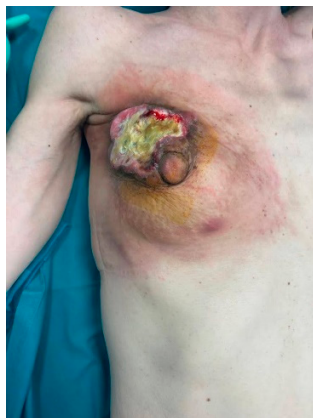


Figure 1. After NAC and NART and before surgery the tumor was locally advanced, with skin ulceration and necrosis.

After three months of the new NAC regimen, breast US showed further increase of the primary neoplasm (48 x 37 mm vs 48 x 18 mm) with skin invasion, and at CT scan no clear cleavage plane of the breast lesion from the pectoralis major muscle was appreciable. Hence, the ongoing NAC regimen was stopped, and it was replaced with Carboplatin every 3 weeks. Breast MR re-evaluation confirmed a clear-cut local PD with a breast mass measuring 64 x 55 x 49 mm with concomitant chest wall infiltration, as indicated by chest CT scan which highlighted tumor invasion of the skin plane, pectoralis major and minor muscles, and intercostal muscles at the 3rd and 4th intercostal spaces; an homolateral axillary lymph node (8 x 6 mm) was also appreciable, and the already detected lymphadenopathy in the right pulmonary hilum was also increased (15 x 15 mm vs 14 x 10 mm).

At this point, on April 2023, the patient came to the attention of our breast unit. After breast and thoracic surgeon's assessment, the lesion was deemed resectable though with a high risk of 3rd rib resection.

Preoperatively, the ulcerated skin of the right breast was sampled for cultural examination with isolation of a multisensitive *Acinetobacter Baumannii*; hence, Amoxicillin/Clavulanate 1 g x 3/day and Metronidazole 500 mg x 3/day antibiotic therapy was given.

On May 2023, the patient underwent Halsted radical mastectomy with partial periosteal resection of the 4th rib, and partial resection of the 3rd and 4th external intercostal muscles (Figures 2 and 3); intraoperative frozen sections were performed and were negative for deep infiltration. However, a precautionary enlargement on the medial, lateral and deep sides of the 4th external intercostal muscle was performed for definitive histology. Intraoperative cultural samples were also undertaken, and again a multisensitive *Acinetobacter Baumannii* was isolated, so that the ongoing antibiotic therapy with Amoxicillin/Clavulanate was replaced by a targeted antibiotic therapy with Meropenem 1 g x 4/day.



Figure 2. The specimen measured 17,5 x 12 x 5 cm.



Figure 3. Local state after Halsted Mastectomy.

Definitive reconstruction was postponed until the findings of cultural examination and definitive histology were available. Moreover, the patient's poor general conditions (BMI = 15,6, albumin 4,1 g/dL, haemoglobin 9,4 g/dL) did not allow a flap reconstruction. In the meanwhile, a negative pressure Vacuum-Assisted Closure (VAC) therapy of 100 mmHg was applied, with subsequent reduction at 80 mmHg due to the patient's poor tolerance (Figure 4). It was maintained for a period of 20 days (Figure 5), during which it was replaced three times, with serial sampling for cultural examination, the last being positive for multiresistant *Staphylococcus Epidermidis* that was treated with Linezolid 600 mg x 2/day in addition to Meropenem.



Figure 4. Local state after application of VAC therapy.



Figure 5. Re-epithelialisation of wound margins after 20 days of VAC therapy.

At definitive histology, G3, ER-negative, PgR-negative, *Ki67* = 90%, c-erb-2 negative invasive ductal carcinoma was diagnosed with free tumor-margins; each specimen of the medial, lateral and deep edges of the 4th external intercostal muscle was free from neoplastic infiltration, as well. Nine lymph nodes were isolated, each of them being negative for the presence of metastases (ypT4b ypN0 Mx, UICC-TNM 2018).

After VAC-therapy a bioengineered dermal matrix (Integra®) placed into the surgical bed (Figure 6). The patient was discharged on the 6th post-operative day, and oral Linezolid 600 mg x 2/day was given until the 10th post-operative day. The dressing was replaced twice a week for a month in the outpatient clinic; hence, the patient underwent a new reconstructive procedure by means of a full-thickness graft taken from the suprapubic region with an abdominoplasty-type design. In the following days, greenish wound secretions were observed, and an infection by *Pseudomonas Aeruginosa* and *Enterobacter Cloacae Complex* was diagnosed; intravenous antibiotic therapy was immediately started giving Piperacillin/Tazobactam 4.5 g x 4/day as empiric antibiotic therapy at first, followed by Ciprofloxacin 750 mg x 2/day and, finally, Ceftolozane/Tazobactam 1.5 g x 3/day.



Figure 6. Application of Integra® matrix.

The applied graft was successful on approximately 40% of the treated surface; there was partial exposure of the 3rd and 4th ribs due to an associated osteomyelitis caused by a multisensitive *Pseudomonas Aeruginosa*; antibiotic therapy with Ceftolozane/Tazobactam was suspended and it was replaced with intravenous Meropenem 1 g x 3/day.

Subsequently, the patient's general conditions and BMI improved, due to a better nutritional intake, so that reconstructive surgery of the chest wall was completed by means of a vertical rectus abdominis pedicled myocutaneous flap (VRAM) to cover the exposed ribs. A local rotation flap was used in the lateral thoracic area to close the infero-lateral loss of substance, and a full thickness dermo-epidermal graft was taken from the medial surface of the right arm, to cover a portion of the aforementioned myocutaneous flap. During the surgical intervention, a sample of periosteal tissue was taken for microbiological examination, which tested again positive for multisensitive *Pseudomonas Aeruginosa*. The Infectious Disease Team suggested an antibiotic therapy with Ceftolozane/Tazobactam 1.5 g x 3/day and Amikacin 900 mg/day. The post-operative course was

uneventful, with an improvement of local conditions and reduction of all inflammatory acute phase proteins. The patient was discharged with intravenous antibiotic therapy at home by means of an elastomeric pump, for a total of four weeks of therapy.

Clinically, she had a progressive improvement at the local site with complete healing being achieved 60 days after the last surgical procedure (Figure 7). Finally, the Patient was in good general condition with no evidence of PD after total-body CT scans, so that no adjuvant post-operative CT was given, and she underwent close follow-up with negative findings until now.



Figure 7. Complete wound healing was achieved 60 days after the last surgical procedure (VRAM, local rotation flap and a full thickness dermo-epidermal graft taken from the medial surface of the right arm).

3. Discussion

This LABC is a complex disease requiring a multidisciplinary approach. A personalized therapeutic approach is mandatory according to tumor biological features, menopausal status, and co-morbidity factors. NAC is usually performed for achieving loco-regional radical resection as well as to reduce the extent of surgery [1,2]. Although the importance of NAC in the multidisciplinary approach to LABC is well recognised, a small number of patients experience only a less than optimal response or even show PD, as in our case, so that breast conserving surgery or even mastectomy may be impossible [3]. PD during NAC for breast cancer is defined as an increase in the tumor size or appearance of new tumor lesions in the breast, lymph nodes, or distant organs [4]. Some trials reported that the rate of PD during NAC is about 3-5% [5,6]. Caudle et Al found that predictors of PD included African American race, large initial tumor size, negative estrogen and progesterone receptor status, high Ki-67 scores, and high nuclear grade [5].

Drug resistance is one of the main causes of therapeutic failure. The best-known drug resistance mechanisms include expression and activity of drug metabolizing enzymes, increased expression levels or enhanced functions of drug efflux systems, overexpression of the Glutathione Detoxification System, the DNA damage repair mechanism, inhibition of cell apoptosis and autophagy, epithelial-to-mesenchymal transition, the activity of exosomes, and the tumor microenvironment. Therefore, one of the more commonly used strategy to overcome drug resistance is to combine multiple chemotherapy drugs. [7].

Whenever PD does occur during NAC treatment, no standard Salvage Treatment (ST) has been defined and different options may be pursued, such as the change of systemic therapies, radiation therapy (alone or in addition to chemotherapy), and surgery [6]. The type of ST is decided by a multidisciplinary team, including medical and radiation oncologist and surgeon. One of the options to face PD during NAC is to switch systemic therapy to a different regimen than initially planned treatment. Another salvage strategy is the use of Neoadjuvant Radiation Therapy (NART), with or without NAC, which has shown in some trials satisfactory results regarding loco-regional control, survival, and post-surgical outcomes [8,9]. Finally, surgery is a feasible approach in patients thought to be operable at the time of PD or in patients treated with non-surgical ST who became operable thereafter. Raphael J et Al found that a significant number of non-operable patients who initially progressed on NAC (69%) were able to undergo surgery after receiving different types of non-

surgical ST [6]. In their trial, upfront surgery, NART alone and NART associated with NAC have been used as ST with approximately the same frequency for patients with hormone-sensitive PD, while upfront surgery was employed as ST in the 72% of the patients with c-erb-2 PD and NART in association with NAC was administered as ST in the 53% of the patients who presented a triple negative PD [6]. No difference in survival was already found between all the ST regimens, even if some clinical results have been promising, providing a starting point for new research [6].

In our case, upfront surgery was not a feasible option at the time of PD, therefore first a systemic therapy switch and then an association of NAC and NART were employed. These ST have made a demolitive but radical surgery possible. Collaboration with thoracic surgeons allowed us to be prepared for a possible resection of part of the chest wall and an eventual repair of substance loss by various reconstructive techniques. The latter procedure was not necessary in view of the absence of disease in the samples of periosteum and intercostal muscles sent to intraoperative frozen section examination.

Following surgical resection of LABC when local PD does occur, as in our case, extensive and complex wounds may require special care because prolonged wound healing can delay adjuvant CT and RT. The achievement of complete wound healing by means of VAC therapy is known to be effective in the management of different complex wounds. It has been shown to improve wound healing by removing excessive interstitial fluid, increasing tissue blood flow, stimulating granulation tissue and neo-vascularization, and decreasing bacterial colonization of wounds, as confirmed in randomized clinical trials [10–14].

The strengths of our work were the multidisciplinary management of the case, which allowed to combine several strategies of ST, and the variety of reconstructive techniques employed accordingly to highly destructive surgery. Moreover, the collaboration with infectious diseases specialists, pain therapists, physiotherapists and nutritionists has allowed to manage in their totality the collateral problems to the patient's main disease. However, as a case report, this article has obvious limitations.

4. Conclusions

LABC is typically an aggressive disease due to adverse biological featured and advanced stage at presentation, with an overall poor prognosis [15]. This case report highlights the importance of a multidisciplinary, tailored treatment for each patient with LABC, especially when PD does occur during NAC. Combination of different medical, radiation, and surgical therapeutic options are welcome with the aim of improving loco-regional and systemic disease control.

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