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Multidisciplinary Management of Locally Advanced Breast Cancer [Version 1, Awaiting Peer Review]

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Abstract

The term "locally advanced breast cancer" (LABC) encompasses a heterogeneous group of breast neoplasms that represent an extremely variable percentage of newly diagnosed breast cancers (4-90%, depending of world regions). These cancers may have different clinical and biological characteristics that can be managed by primary surgery or neoadjuvant integrated treatments. In this paper we review the updated guidelines and discuss most recently reported evidence related to LABC multidisciplinary workout, in order to maximize results of combined systemic therapies, modern surgical procedures and radiotherapy.

Introduction

The term locally advanced breast cancer (LABC) encompasses a heterogeneous group of breast neoplasms. In the last revision of the American Joint Committee on Cancer (AJCC) staging system, all of stage III disease is considered locally advanced, including cases with clinical stage IIB disease, such as primary tumor ≥5 cm and no nodal involvement (T3 N0); stage IIB–IIIA (T3 N0–1) considered as 'large operable' breast cancers and truly inoperable cases with involvement of supraclavicular or internal mammary nodal involvement (T4N2-3) and inflammatory breast cancer (IBC) featuring marked neoangiogenesis, high grade, aneuploid features, hormone-receptor negative status, high S-phase fraction and p53 mutations and a severe prognosis (Figure 1) [1-3].

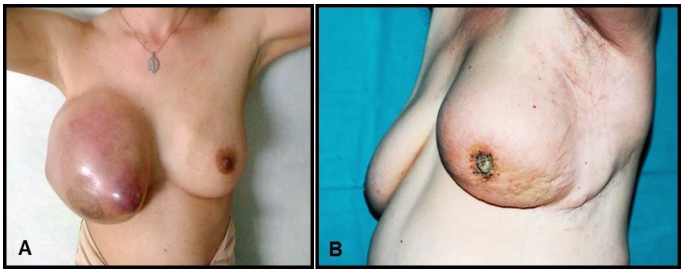

Figure 1: Inoperable LABC. (A) Patient with giant papillary carcinoma of the right breast determining a diffuse ulcerative and inflamatory clinical presentation (B) Massive inflamatory carcinoma of the left breast with diffuse <<peasu d' orange>> and nipple areola complex ulceration.

In screened populations, the use of mammography and increased public awareness of breast cancer have resulted in women having smaller tumors and fewer involved nodes at the time of initial presentation. As a matter of fact, data obtained from National Cancer Database and the CONCORD high-resolution study in Europe indicate that approximately 8.5% of American and 4% of European patients with breast cancer present with LABC [4].

Nevertheless, LABC still remains an important and challenging theraputical issue, especially in low- to middle-income countries where its incidence can reach 90% of newly diagnosed breast cancers [5].

This Review describes the current treatment options for the management of patients with LABC.

Clinical Features

According to the 2016 National Comprehensive Cancer Network (NCCN) Guidelines, LABC can be stratified inoperable LABC (clinical TNM stage T3, N1, M0) and inoperable LABC (clinical stage IIIA [except for T3, N1, M0], clinical stage IIIB or clinical stage IIIC) [6]

Diagnosis

In LABC workout, breast imaging is essential. Bilateral mammography and breast ultrasound (BU) should be performed as clinically warranted, as they can help to delineate the size and configuration of the primary breast tumor. Execution of Mammography determine the extent of any malignant microcalcifications that may indicate an extensive intraductal component [7], but may be inappropriate for patients with gross presentations of LABC (bleeding or fungating tumour), in which ultrasound is a valuable method in assessing tumor size and extent, before initiation of treatment.

In such setting, magnetic resonance imaging (MRI) is an important tool to integrate important information as axillary/internal mammary nodal status, pectoralis fascia/skin infiltration and real extent of breast cancer (infiltrative or in situ components) as well as in monitoring response to Neoadjuvant chemotherapy [8-10].

If standard imaging results equivocal or suspicious, fluorine 18 fluorodeoxyglucose - positron emission tomography computed tomography (FDG PET/CT) can be most helpful and its diagnostic power can be also used to detect regional node involvement as well as distant metastases in LABC including T3 N1 disease [11,12]

The diagnosis of LABC must be confirmed with core needle biopsy or fine needle biopsy. A core biopsy has the advantage of obtaining sufficient material to characterise the tumour (even on breast cancer, but also on suspected lymph nodes) in terms of grade, hormone receptor status, proliferation index (Ki-67) and HER-2 status.

Furthermore, a genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer [13].

Treatment

Operable LABC (clinical stage T3, N1, M0)

A subset of invasive breast cancers where the initial clinical and radiologic evaluation describe a disease to the breast and regional lymph nodes.

Were a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control, patients can be treated by means of breast conserving surgery (BCS) using oncoplastic procedures (OPP), that associating principles of surgical oncology with the best principles of reconstructive surgery have shown to optimize oncologic safety and cosmetic outcomes [14,15].

Conversely, candidates to primary mastectomy can be treated as nonoperable LABC patients, by means of neoadjuvant chemotherapy (NAC).

Even though NAC does not improve disease or overall survival, it does produce a shrinkage of the tumor in a variable percentage between 20 and 40% of patients, according to its histology (lobular or ductal carcinoma) and biological characteristics [16] thus allowing BCS execution in cases that would have required a mastectomy (Figure 2) [17,18].

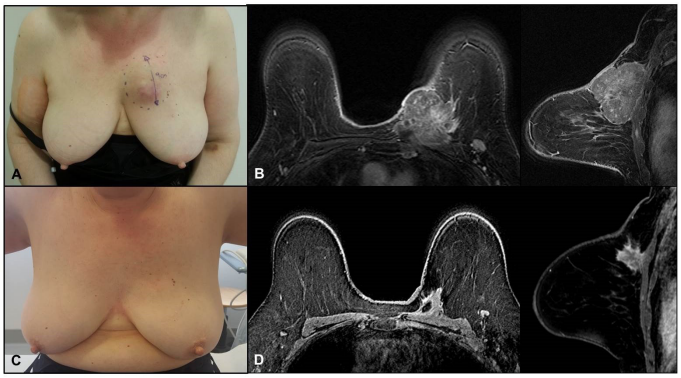

Figure 2: Clinical major response to NAC for nonoperable LABC. (A) Patient presenting with a massive T4 ductal carcinoma of the left breast with skin infiltration (B) Magnetic resonance reconstructions, confirming a 9cm left breast malignant neoplasm, infiltrating pectoralis fascia and overlying skin. (V) Apparent clinical complete response (D) Magnetic resonance reconstructions, that showed a significative neoplasm reduction and fragmentation (9cm to a maximum diameter of 1cm foci) without infiltration of the pectoralis fascia and overlying skin.

Before NAC, careful consideration should be given to the potential future need to identify the exact original tumor location if there is a complete clinical and radiological response. This is now performed routinely by inserting a radiopaque marker under mammographic, sonographic, or MRI guidance [19,20].

In cases of pCR, such marker placement allows the pathologist to scrutinize that particular area in search of residual tumor.

Inoperable LABC (clinical stage IIIA [except for T3, N1, M0], clinical stage IIIB or clinical stage IIIC)

The combination of systemic therapy, surgery and radiotherapy in inoperable LABC is mandatory, and although the optimal administration sequence has not been established through clinical trials, initial systemic treatment is believed to be advantageous as it can increase resectability and breast conservation rates without compromising survival outcomes [21].

Neoadjuvant Chemotherapy

Anthracycline and taxane-based regimens are the standard primary neoadjuvant chemotherapy for LABC [13, 22], as it was shown that the addition of sequential taxanes resulted in a significantly enhanced clinical response rate (94% vs. 66%) and a substantially increased complete histopathological response rate (34% vs. 16%) thus enhancing BCS rates (67% vs. 48%), when compared to patients receiving anthracycline-based therapy alone [23].

Furthermore, the addition of taxanes to an anthracycline-based regimen leads to higher and improved overall survival [24].

For patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, a HER2-directed agent (eg, trastuzumab with or without pertuzumab) should be added to the chemotherapy regimen.

All trials of trastuzumab added to NAC in patients with HER2-positive breast cancer, have demonstrated a significant increase in pathological complete response rate, from 18% in patients not receiving Trastuzumab to 65% in patients who received Trastuzumab. Thus, the combination of trastuzumab plus cytotoxic therapy currently constitutes the standard treatment for women with HER2-positive LABC [25-28].

Several studies have evaluated the effect of treating patients with breast cancer with trastuzumab in combination with another anti-HER2 agent, such as pertuzumab.

In the phase II NeoSphere trial, in which patients with early, locally advanced and inflammatory HER2-positive breast cancer were randomly assigned to receive trastuzumab plus docetaxel, pertuzumab and trastuzumab plus docetaxel, pertuzumab and trastuzumab, or pertuzumab plus docetaxel, pathologically complete response rates were significantly improved with the addition of dual HER2 blockade to chemotherapy (29%, 46%, 17% and 24%, respectively) [29].

In a recent randomized phase II study, patients with phenotypically luminal tumours were randomized to neoadjuvant chemotherapy or neoadjuvant endocrine therapy. MRI assessment of response rate in premenopausal patients was lower with hormonal treatment (75% versus 44%); such a difference was not seen in the postmenopausal population [30].

These data suggest that neoadjuvant endocrine therapy should not be administered in premenopausal women and that preoperative endocrine therapy should be reserved for slow growing, often neglected, LABC as well as for elderly patients or those with significant co-morbidities.

Aromatase inhibitors have been shown to be the best preoperative endocrine therapy for postmenopausal patients. Both letrozole and anastrozole have demonstrated response rates significantly superior to tamoxifen in patients being treated preoperatively, including those with LABC and IBC [31,32].

Breast Surgery after NAC

Surgical therapy following clinical response to systemic therapy usually consists in total mastectomy and reconstruction or (if feasible) lumpectomy, ever associated with axillary staging (level I/II dissection).

Several randomized clinical trials have shown that NAC converts a proportion of patients who require mastectomy because of large primary tumors or an unfavorable tumor size/breast size ratio to candidates for breast-conserving surgery and oncoplastic surgery without significantly increasing the rates of ipsilateral breast tumor recurrence (IBTR) [33, 34].

In patients who experience a clinical response to NAC, oncoplastic surgical techniques have shown to optimize cosmetic outcomes by implementing the best principles of plastic surgery in order to achieve wide tumor-free margins [35] even by the innovative use of fillers that can be used in association to very wide resections, in order to optimize cosmetic results and reduce the risk of postoperative haematoma and infections (Figure 3) [36-38]

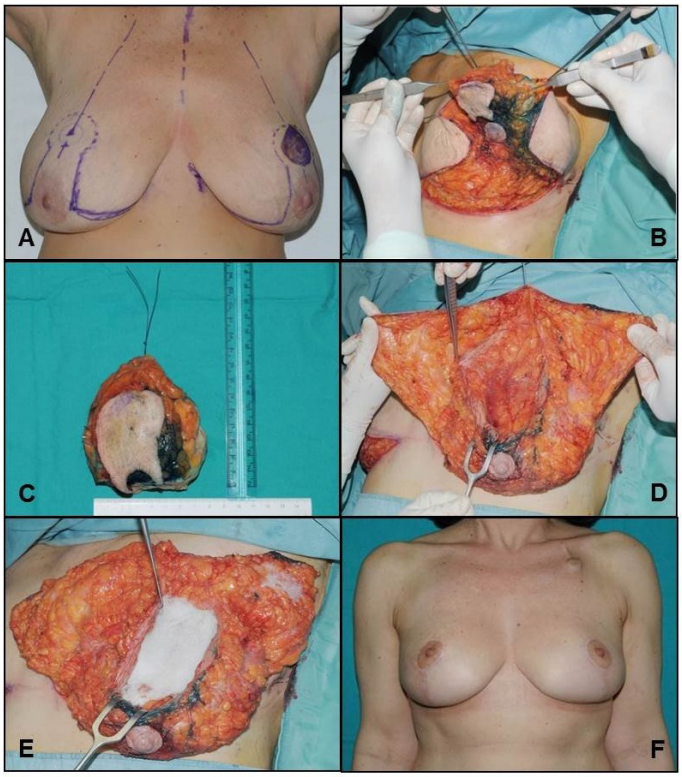

Figure 3: Oncoplastic procedure of quadrant ectomy with reduction mammaplasty following QUORC technique. (A) Tailored preoperative planning (B) Upper quardant ectomy with 40% of glandular tissue excision en bloc with the skin overlying the lesion (C) 8X8 cm surgical specimen (D) Surgical field after quadrant ectomy (E) Oxidized regenerated cellulose layers positioning (F) Cosmetic result 12 months after surgery.

Axillary Staging after NAC

There is strong evidence that NAC downstages involved axillary lymph nodes in a considerable proportion of patients (up to 30 % with anthracycline-containing regimens [39], up to 40 % with anthracycline/taxane-containing regimFens [40] and even at higher rates for HER2/neu-positive patients who are treated with NC plus anti-HER2/neu therapy) [41-43].

Unfortunately, after receiving NAC, this outsanding axillary results are not followed by mininvasive axillary staging, as there is still too much controversy on this issue.

Two recently published prospective multicentre trials (the German SENTINA (SENTinel NeoAdjuvant) [44] study and the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial) [45] seemed to definitively contraindicate SLNB after NACT.

According to these relevant evidences, SLNB showed the best detection rate only if performed prior to neoadjuvant therapy (99.1%) and an extremely wide detection variability (60.8 - 92.9%) when performed after NAC.

Even FNR of SNLB if performed after NACT showed extremely variable results: the best reported is 12.6%, but it has to be clearly stated that if only one SLN was detected, the FNR increases up to 24.3-31% [44, 45].

Conversely, two recent meta-analyses concluded that SLNB is a reliable tool for planning treatment for patients treated with NC as an alternative to completion axillary lymph node dissection [46,47].

And that SLNB was also feasible after NAC in node-positive breast cancer patients, although the false-negative rate was high and requires addressing [48].

According to these results, current guidelines do not offer an univocal behavior and still advise for SLNB or a level I/II ALND in patients who are proven node positive prior to NACT, with minimal concern of the result of the SLNB if performed after NACT, thus excluding from mininvasive advantages patients who benefit of NACT, achieving a complete axillary response and exposing them to an approximately threefold risen risk of surgical morbidities [49].

Adjuvant Radiotherapy

Radiation schedules and doses vary among institutions; nonetheless, it is generally agreed that in patients for whom postoperative chemotherapy is not planned (including those given NAC), radiotherapy should start approximately 4 to 6 weeks after surgery and should be delivered to the entire breast and/or chest wall. Standard dosing schedules incorporating 50 to 50.4 Gy in 1.8–2 Gy fractions have recently been widely replaced by a hypofractionated regimen of 40–42.5 Gy in 15–17 fractions [50-52].

If breast-conserving therapy is performed, it should be followed by a boost of 10–18 Gy to the tumour bed, even after NAC [53].

Nodal irradiation was associated with significantly increased disaease free and overall survival, although the relative role of irradiation of particular nodal areas is not clear [54].

Conclusions

Although screening programs and breast tumor awareness has resulted in a progressive decrease in LABC diagnosis, it still remains a difficult clinical problem due to the lacking of uniform evidences and the difficulties in disease control, obtaining low rates of relapse and high rates of overall survival.

As a matter of fact, the term LABC encompasses patients with large, but operable primary tumors and patients with rapidly progressing inflammatory carcinomas, who have very different prognoses. Thus, treatment decisions must be tailored to the individual patient. Every LABC patient needs multidisciplinary assessment and coordination of care among radiology, pathology, plastic surgery, medical oncology, surgical oncology and radiation oncology.

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