Update in the treatment of locally advanced breast cancer: a multidisciplinary approach

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Abstract. – Locally advanced breast cancer represents a wide variety of neoplasms and constitutes approximately 10%-20% of the newly diagnosed breast cancers. These cancers may have widely different clinical and biological characteristics. According to the American Joint Committee on Cancer (AJCC) staging system, all of stage III disease is considered locally advanced.

The clinical treatment of locally advanced breast cancer is complex and should be tailored to the individual patient. In this paper we discuss the options of management of locally advanced breast cancer, focusing on a multidisciplinary approach through a combined-modality care involving surgery, radiotherapy and systemic therapy.

Key Words: Breast cancer, Management, Multidisciplinary approach.

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 involvement of supraclavicular lymph nodes and which often are initially inoperable (T4N2-3). The same applies to 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.$^1\text{-}^3$

LABC constitutes up to 20% of breast cancer in medically underserved populations in the United States and up to 75% of breast cancers in developing countries.$^4\text{-}^7$

These cancers vary widely in biological characteristics and clinical behavior, ranging from locally aggressive, but systemically “indolent”, to de novo generalized disease.

The prognosis depends on tumor size, extent of lymph node involvement, and the presence or absence of an inflammatory component. According to the SEER data (1973-1998), the 3- and 5-year relative survival rates for women with stage III breast cancer are 70% and 55%, respectively. Median survival for women with stage III disease is 4.9 years.

The clinical management of LABC is complex and should be tailored to the individual patient. A multidisciplinary approach is recommended combining surgery, radiotherapy and systemic therapy (chemotherapy and/or hormone therapy).

Clinical Features

Locally Advanced Breast Cancer

Locally advanced breast cancer is a heterogeneous disease, including disease which is either extensive within the breast and/or ipsilateral nodal areas (Figures 1, 2, 3). Staging is based on the TNM (tumour, nodes, metastasis) system (Table I). The staging system for breast cancer has varied over time, so categorisation of LABC varies subtly between studies. Some studies of LABC include patients with large tumours, e.g. > 5 cm in size. However, the size of the primary tumour on its own does not qualify a tumour for LABC status. These differing definitions may make comparison of results between studies difficult.

Inflammatory Breast Cancer

Inflammatory breast cancer (Figure 4) is characterised by rapid onset of diffuse erythe-
ma and warmth, oedema of most of the breast often with breast enlargement, diffuse firmness on palpation, one breast is often ‘heavier’ than the other peau d’orange and ridging. Peau d’orange is not uncommon after treatment for breast cancer (surgery and radiotherapy), but in this case it usually improves with time. These features may also be seen with mastitis or a breast abscess. Consequently, patients with inflammatory breast cancer are often initially thought to have infection and are often referred when the signs have not responded to treatment with antibiotics. A discrete mass may not be present.

**Locally advanced breast cancer is defined as:**
- T3 N2-3 M0
- T4 N any M0
- T any N any M 1(scf)

**T = Tumour**
- T1 Tumour ≤ 2 cm
- T2 Tumour > 2 cm ≤ 5 cm in greatest diameter
- T3 Tumour > 5 cm in greatest diameter
- T4a Extension to chest wall (ribs, intercostal muscles, serratus anterior but not pectoral muscles)
- T4b Oedema (peau d’orange), ulceration of skin of breast, satellite nodules
- T4c Both T4a and T4b
- TM Inflammatory carcinoma

**N = Nodes**
- N0 No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary lymph nodes
- N2a Involved axillary nodes fixed to one another or other structures,
- N2b Metastasis in clinically apparent ipsilateral internal mammary nodes (in absence of clinically evident axillary nodes)
- N3a Metastasis to infraclavicular node(s)
- N3b Metastasis in internal mammary and axillary node(s)
- N3c Metastases in supraclavicular node(s)

**M = Metastasis**
- M0 No distant metastasis
- M1(scf) Metastasis only to ipsilateral supraclavicular lymph nodes
- M1 Distant metastasis
Diagnosis

Breast imaging is essential for all women presenting with significant breast symptoms. Mammography and ultrasound however, may not demonstrate the classic features of primary breast cancer in IBC. For instance, imaging may show nonspecific signs such as generalised increase in breast tissue density and thickening of the skin rather than a discrete lesion. It would not be unusual to find significant clinical signs with minimal radiological abnormality, but at other times the imaging findings may be quite obvious. Mammography may be inappropriate for patients with gross presentations of LABC (bleeding or fungating tumour), although ultrasound is a valuable method of documenting tumour size and extent before initiation of treatment.

A computed tomography and dynamic magnetic resonance imaging must be used to study the breast and lymph-nodal areas. The diagnosis of LABC or IBC can be confirmed with core needle biopsy or fine needle biopsy. A core biopsy has the advantage of obtaining sufficient material to characterise the tumour in terms of grade, hormone receptor status and HER-2 status.

Treatment of Operable Tumours (Stage IIIA)

Patients with stage IIIA breast cancer have traditionally been treated with modified radical mastectomy (MRM) followed by adjuvant systemic therapy and radiotherapy. In the last decade neoadjuvant chemotherapy (NAC) followed by surgery and radiotherapy has progressively become the standard approach.

Management of operable tumors (IIIA)

- MRM followed by chemotherapy and locoregional radiotherapy
- Chemotherapy first followed by surgery and locoregional radiotherapy

Even though NAC does not improve disease or overall survival, it does produce in many cases a shrinkage of the tumour allowing the performance of breast-conserving surgery (BCS), in cases that would have required a mastectomy.

The reported response rate following NAC for operable breast cancer in randomized clinical trials varies between 49 and 94%, with a pathologic complete response (pCR) rate of 4-34%.

Anthracycline based regimens were been widely used, but recent studies indicate a response rate at least equivalent better using taxanes as single agent or in combination. The largest study using neoadjuvant docetaxel (NS-ABP B-27) showed pCR in 26% of patients who received four cycles of docetaxel following four cycles of adriamycin–cyclophosphamide compared with 14% in those receiving four cycles of adriamycin–cyclophosphamide only. In many randomized studies reported, breast-conserving surgery could be carried out following NAC in 22-82% of patients with IIIA LABC. The lowest rate of breast conservation was the EORTC 10902 trial in which only 22% of patients had breast-conserving surgery. Scholl et al demonstrated an 82% breast conservation rate initially following NAC and radiotherapy. However, the rate decreased to 61% at 5 years because of the development of local recurrence treated by subsequent mastectomy.

More recently, new drugs have been introduced in the routine treatment of locally advanced breast cancers, even in neoadjuvant setting; among them, Trastuzumab, a humanized monoclonal antibody directed to the extracellular domain of the HER-2 receptor, has showed encouraging results.

Mohsin et al carried out a prospective trial involving 35 patients with LABC overexpressing Her-2/neu, in the attempt to identify predictive clinical markers of response to the antibody. Patients received weekly trastuzumab as a single agent for the first 3 weeks, and then combined with docetaxel for 12 weeks before surgery. The authors reported an early response to trastuzumab as monotherapy, with a median tumour de-
crease of 20%. Eight patients showed a partial response. The study suggests that one of the mechanisms of action is apoptosis. The apoptotic mechanism may result in a synergistic or additive activity when it is combined with chemotherapy. In fact, resistance to chemotherapy-induced cell death may be overcome by a drug that works on a common antiapoptotic pathway. Chemotherapy may exert an additive effect by killing the more rapidly proliferating cells\textsuperscript{14-16}. A recent trial of neoadjuvant chemotherapy in HER-2 positive tumours compared paclitaxel followed by FEC (fluorouracil, epirubicin, and cyclophosphamide) chemotherapy to paclitaxel, FEC, and trastuzumab (Herceptin). Forty-two patients with T1-3 N0-1 tumours were evaluated with a median follow-up of 20 months. The results showed the regimen including trastuzumab to be so superior that the trial was stopped\textsuperscript{10}.

Bianchi et al\textsuperscript{17} showed that trastuzumab appears to be highly effective when given concomitantly with doxorubicin and paclitaxel (AT) or with paclitaxel alone after completion of AT in the treatment of locally advanced breast cancer. The findings of this study justified the recent initiation of a multicenter, randomized, controlled Phase III trial comparing AT followed by paclitaxel then by CMF with the same chemotherapy plus trastuzumab in women with HER2-positive locally advanced breast cancer.

NOAH (NeOAdjuvant Herceptin) is a Phase III trial of neoadjuvant trastuzumab in combination with chemotherapy in patients with HER2-positive locally advanced breast cancer. In this study, Gianni et al showed that Neoadjuvant Herceptin plus AT/CMF-containing chemotherapy significantly improved the pCR rate of LABC vs chemotherapy alone. Treatment was well tolerated with acceptable cardiac safety. Follow-up is ongoing and EFS is maturing\textsuperscript{19}.

Geyer et al\textsuperscript{19} studied the Lapatinib, a tyrosine kinase inhibitor of human epidermal growth factor receptor type 2 and epidermal growth factor receptor. They compared lapatinib plus capecitabine with capecitabine alone in such patients. Women with HER2-positive, locally advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab were randomly assigned to receive either combination therapy (lapatinib at a dose of 1250 mg per day continuously plus capecitabine at a dose of 2000 mg per square meter of body-surface area on days 1 through 14 of a 21-day cycle) or monotherapy (capecitabine alone at a dose of 2500 mg per square meter on days 1 through 14 of a 21-day cycle). They showed that lapatinib plus capecitabine is superior to capecitabine alone in women with HER2-positive advanced breast cancer that has progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab\textsuperscript{16,19}.

Accurate monitoring of the response to therapy should be adopted in all patients undergoing NAC. Magnetic resonance imaging (MRI) has been shown to be most accurate of the currently available methods for assessment of residual disease after NAC, as mammography and ultrasonography may not be able clearly to distinguish chemotherapy-induced fibrosis from residual tumour. At surgery, it may be difficult to identify the exact tumour location following a complete clinical response to NAC. A good option is to consider insertion of tissue marker clips into the tumour at the time of biopsy to enable preoperative localization of the tumour bed in the event of a complete clinical response\textsuperscript{20,21}.

Tumour response following NAC has been shown to be either concentric or honeycombed. In the latter instance, the tumour shrinkage is uneven and viable tumour foci may remain some distance away from the central residual tumour site. This may account for the reported higher local recurrence rates observed in some of the randomized trials. Detailed histopathological assessment of margins is essential in such patients. If there is any evidence of multifocal disease, re-excision or mastectomy should be considered.

The results from two trials (NSABP B 18 and EORTC trial) suggested that patients whose tumours were down-staged so that BCS could be performed when it was not initially planned were at higher risk of local recurrence and had worse survival. So, patient with operable stage III disease who desires to preserve their breast should be made aware that BCS may expose to this risk\textsuperscript{22-28}.

MRM remains the standard surgical treatment for operable locally advanced disease that have suboptimal clinical response to NAC. Breast reconstruction should be delayed after completion of chemotherapy and radiotherapy.

The role of radiotherapy to locoregional management was investigated in many studies. In the study of Olson et al, eligible patients with operable LABC had a mastectomy, 6 cycles of anthracycline-based chemotherapy and, if disease-free, were randomly assigned to receive radiotherapy or observation with radiotherapy at isolated sites.
of locoregional failure\textsuperscript{29}. Locoregional recurrences were reduced from 24\% to 15\% with immediate radiotherapy\textsuperscript{29}.

When locoregional radiotherapy is delivered following MRM for locally advanced disease, radiation should be delivered to the chest wall and the supraclavicular and axillary nodes. Whether treatment to the internal mammary nodes is required is unclear. In many studies the internal mammary nodes were irradiated. However, there are no studies that examined the impact of such radiotherapy. It is not unreasonable to include radiotherapy to the internal mammary nodal region, provided that this can be done without treating an excessive amount of heart or lung tissue.

\textbf{Treatment of Inoperable Tumours (Stage IIB-IIIC)}

Patients with stage IIB or IIC disease, including those with inflammatory breast cancer and those with isolated ipsilateral internal mammary or supraclavicular lymph-node involvement are often inoperable.

Patients with stage IIB or IIC disease who respond to primary chemotherapy should be treated until the response plateaux or to a maximum of 6 cycles (minimum 4 cycles) after which several case series have demonstrated that locoregional control is improved\textsuperscript{30-35}.

The locoregional management of patients with stage IIC disease who respond to chemotherapy is unclear and should be individualized. In the absence of evidence on this subgroup of patients, it is reasonable that they receive locoregional radiotherapy (including nodal irradiation). The role of completion mastectomy should be individualized and based on technical and disease factors\textsuperscript{28-33}.

The treatment of patients with LABC whose tumours do not respond to anthracycline-containing chemotherapy is unclear.

It is reasonable to try taxane chemotherapy or to proceed directly to locoregional therapy including irradiation and MRM, if possible\textsuperscript{28-33}.

Following completion of chemotherapy, pre- or postmenopausal patients with locally advanced (operable and inoperable) hormone-responsive tumours should receive adjuvant tamoxifen therapy, 20 mg/d, for 5 years. Tamoxifen should be started after completion of chemotherapy. Patients who are not candidates for any chemotherapy can be managed with hormonal treatment and then receive locoregional management\textsuperscript{36-39}.

\textbf{Conclusion}

The clinical management of LABC is complex and should be tailored to the individual patient. Locally advanced breast cancer and IBC present diagnostic and management challenges. Inflammatory breast cancer in particular, may be difficult to diagnose and is often mistaken for mastitis. Persistent inflammatory symptoms must therefore be investigated and referred to a breast surgeon if not responding as expected to antibiotic therapy. Treatment of LABC and IBC requires a coordinated multidisciplinary approach that should be individualised depending on tumour characteristics and response to treatment. The treatment may include a combination of chemotherapy, radiotherapy and surgery. While the prognosis in these cases is poor compared to that for other presentations of breast cancer, a reasonable survival and quality of life can be obtained with a team approach to treatment. New technologies such as complementary DNA microarrays, genomics and proteomics should help clinicians to better characterize the biology of breast cancer and to tailor treatment based on distinct molecular profiles with prognostic and predictive value.

\textbf{References}


