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OVERVIEW ON LOCALLY ADVANCED BREAST CANCER: DEFINING, EPIDEMIOLOGY, AND OVERVIEW ON NEOADJUVANT THERAPY

B. Yalcin

Department of Medical Oncology, Yildirim Beyazit University, Faculty of Medicine, Ankara 06590, Turkey

According to the analysis on locally advanced breast cancer (LABC) from all breast cancer cases recorded in Surveillance Epidemiology and End Results database between the years 1992–1999 in the United States, the incidence of LABC were found to be 4.6% of all female breast cancers. Clinically, when breast cancer has advanced locoregionally but has not yet spread outside of the breast and regional lymph nodes, it is considered LABC. LABC includes breast cancers that have evidence of a large mass, involve the skin of the breast or the underlying muscles of the chest wall, and cancers that have infiltrated into the local lymph nodes. The prognosis of patients with LABC is relatively poor, with 5-year survival rates less than 50%. Because the incidence of LABC is very low, there are not many studies comparing neoadjuvant chemotherapy regimens in the literature. In management of LABC, initial therapy should be systemic neoadjuvant chemotherapy, aiming pCR. Anthracycline-based chemotherapy regimens are frequently recommended as the standard primary neoadjuvant chemotherapy for the treatment of LABC. Today, the optimal duration of neoadjuvant chemotherapy is unknown. Neoadjuvant endocrine therapy is considered an option for patients with hormone receptor-positive LABC. Ongoing clinical trials are now under way to evaluate the use of novel targeted agents in the neoadjuvant treatment of LABC.

***Key Words*: breast cancer, epidemiology, locally advanced, neoadjuvant therapy.**

DEFINING OF LOCALLY ADVANCED BREAST CANCER

Clinically, when breast cancer has advanced locoregionally but has not yet spread outside of the breast and regional lymph nodes, it is considered locally advanced breast cancer (LABC). In addition, LABC includes breast cancers that have evidence of a large mass, involve the skin of the breast or the underlying muscles of the chest wall, and cancers that have infiltrated into the local lymph nodes. Many cases of LABC have a tumor mass that is both palpable and visible, although some patients have a more diffusely infiltrated tumor without a dominant mass. Generally, an obvious tumor mass (bigger than 5 cm) is occurred on mammography. In any case, the initial evaluation of patient must include careful palpation of the skin, breasts, and locoregional lymph nodes.

In terms of the American Joint Committee on Cancer "TNM staging system", LABC is defined as stage III disease and is represented by stage IIIA (T0N2M0; T1/2N2M0; T3N1/2M0), stage IIIB (T4N0–2M0), and stage IIIC (TanyN3M0) [1]. Among these forms of LABC, stage IIIA (T3N1M0) patients are considered to have surgical resectable LABC, whereas all other forms of LABC is considered inoperable. Furthermore, a growing subset of LABC, termed inflammatory breast cancer (IBC), is becoming increasingly diagnosed. The prognosis of patients with LABC and especially IBC is relatively poor, with 5-year survival rates less than 50%.

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Correspondence: E-mail: bulyalcin@yahoo.com
Abbreviations used: AC – doxorubicin plus cyclophosphamide; CI – confidence interval; HER-2 – human epidermal growth factor 2; IBC – inflammatory breast cancer; LABC – locally advanced breast cancer; pCR – pathological complete response; SEER – Surveillance Epidemiology and End Results.

EPIDEMIOLOGY

According to the analysis on LABC from all breast cancer cases recorded in Surveillance Epidemiology and End Results (SEER) database between the years 1992–1999 in the United States, the incidence of LABC were found to be 4.6% of all female breast cancers [2]. In this group the mean age at diagnosis was reported as 60.6 years. Another analysis of the SEER database from 1988–2000 (n = 180,224) demonstrated that the age-adjusted incidence rates of LABC declined significantly from 1988–1990 to 1997–1999 (from 2.5 to 2.0 cases/100,000 woman-years; $p = 0.0025$) [3]. Comparing white women, black women had a higher risk of being diagnosed with LABC (relative risk 1.8; 95% confidence interval (CI) 1.7–2.0). Also, the risk of presenting with larger breast mass (>2.0 cm) was found in this group, comparing those with smaller mass (<2.0 cm) (relative risk 5.4; 95% CI 4.9–6.0).

OVERVIEW ON SYSTEMIC NEOADJUVANT CHEMOTHERAPY

Because the incidence of LABC is very low, there are not many studies comparing neoadjuvant chemotherapy regimens in the literature. Fortunately, in neoadjuvant chemotherapy setting there was two published randomized studies [4, 5]. The results of these studies showed that achieving a pathological complete response (pCR) with neoadjuvant therapy is considered an important endpoint for survival advantages in patients with primary operable early-stage breast cancer. In management of LABC, initial therapy should be systemic neoadjuvant chemotherapy, aiming pCR [6].

The NSABP B-18 clinical trial randomized 1523 patients with primary operable early stage breast cancer, to preoperative or postoperative treatment with doxorubicin plus cyclophosphamide (AC) [7]. After a 9-year follow-up, investigators reported no sig-

nificant difference in overall survival or disease-free survival between two groups [8]. In addition this, there was a significant association between reaching a pCR and outcome. Patients with a pCR had a 50% reduction in the risk of death compared with the overall patient group (relative risk 0.50; 95% CI 0.32–0.78), adjusting for other factors. Then, NSABP B-27 study was started to evaluate the addition of a taxane to neoadjuvant chemotherapy [9]. This study randomized 2411 patients with primary operable breast cancer to receive AC with or without subsequent docetaxel before surgery; a third arm administered neoadjuvant AC followed by surgery followed by adjuvant docetaxel. After a median follow-up of 6.5 years, there was again no significant difference in either disease-free survival or overall survival, in terms of adding docetaxel to therapy. The rate of pCR was higher in adding docetaxel group than AC group (26.1% *vs.* 12.9%; $p < 0.0001$). Also, it has been showed that the pCR is an important predictor for improved disease-free survival (hazard ratio 0.45; $p < 0.0001$) and overall survival (hazard ratio 0.33; 95% CI 0.23–0.47; $p < 0.0001$). After then, Rastogi et al. emphasized that the importance of achieving a pCR and its later impact on survival [10].

Lately, it has been showed that pCR following neoadjuvant concomitant paclitaxel and radiotherapy was improved both disease-free survival and overall survival [11]. In a pathological biomarkers study evaluated for predicting of pCR, histological grade and hormone receptor were only independently predictive factors in treatment of docetaxel plus epirubicin in neoadjuvant setting, whereas, Ki-67 index, HER2, and cyclin D1 were not [12].

NEOADJUVANT SYSTEMIC CHEMOTHERAPY

Generally, anthracycline-based chemotherapy regimens are recommended as the standard primary neoadjuvant chemotherapy for the treatment of LABC. Frequently, doxorubicin is combined with cyclophosphamide and 5-fluorouracil in this setting. Also, it has been demonstrated the efficacy of the addition of a taxane to anthracycline-based therapy as neoadjuvant therapy [13]. In this study, 162 patients with LABC were treated with preoperative doxorubicin plus cyclophosphamide plus vincristine and prednisolone. Responders to the therapy were randomized to either continue this chemotherapy regimen or switched to receive docetaxel. Higher rates of pCR were observed in switched to docetaxel group, comparing other group (34% *vs.* 16%; $p = 0.04$). Also, the 3-year overall survival rate as well as a higher frequency of breast conserving surgery (67% *vs.* 48%) in taxane group [14].

DURATION OF NEOADJUVANT CHEMOTHERAPY

Today, the optimal duration of neoadjuvant chemotherapy is unknown. Traditionally, the standard anthracycline-based regimen was administered for a minimum of 3–4 cycles, until 2 cycles beyond when a maximal clinical response was reached. However, the TAX-301 trial was consisting of switching over to a taxane after receiving 4 cycles of the initial anthracycline-based treatment [13]. For addressing this the GeparTrio phase III trial was conducted [15]. In this study, 2090 patients were treated with two 3-week cycles of doxorubicin plus cyclophosphamide plus docetaxel. Responders (n = 1390) were randomized to receive either 4 or 6 more cycles of the same regimen (for a total of 6 or 8 cycles). In both groups the rate of pCR was statistically similar. However, adverse events were associated in the 8-cycle group.

The anti-HER2 monoclonal antibody, trastuzumab has been studied as a monotherapy in the neoadjuvant setting in LABC. The first study was done in 35 patients with HER2-positive LABC. The treatment of the patients was started with single-agent trastuzumab, followed by a combination of trastuzumab plus docetaxel prior to surgery [16]. And then, Horiguchi et al. found the rate of pCR or near pCR of 41.2%, and a 3-year overall survival rate of 88%, in HER2 (+) patients treated with the combination of paclitaxel and trastuzumab regimen [17]. Other small study showed that the pCR rate with the combination of trastuzumab with docetaxel plus vinorelbine was 39% in HER2 (+) LABC patients [18].

Based on these findings, the NOAH trial, a randomized controlled superiority trial with parallel HER2-negative cohort, was planned. Aim of this study was evaluated the neoadjuvant chemotherapy (doxorubicin plus paclitaxel followed by paclitaxel plus cyclophosphamide/methotrexate/5-fluorouracil) with or without concomitant trastuzumab over 1 year prior to surgery in 226 HER2 (+) patients. The 3-year event-free survival was found significantly higher in the trastuzumab group (71% *vs.* 56%; hazard ratio 0.59; 95% CI: 0.38–0.90; $p = 0.013$) [19]. Another trial, the GeparQuattro study evaluated neoadjuvant trastuzumab given concomitantly with anthracycline/taxane-based chemotherapy in the patients with HER2 (+). The investigators reported that the rate of pCR among HER2-positive patients was 31.7% [20].

These data suggest that neoadjuvant trastuzumab combined with chemotherapy should be a standard therapeutic option in women with HER2-positive LABC.

NEOADJUVANT HORMONAL THERAPY

Neoadjuvant endocrine therapy is considered an option for patients with hormone receptor-positive LABC. This may be an alternative to cytotoxic systemic chemotherapy, especially for older patients and/or existing comorbid conditions. In a study of 47 patients with LABC and comorbid illness, after 6 months neoadjuvant tamoxifen treatment, the response rate was reported as 47%, and disease-free survival rate at 40 months was found 49% [21]. Chia et al. have been reported that neoadjuvant tamoxifen therapy decreases the overall tumor burden in one half of LABC patients, although the rate of pCR appears to be lower than given chemotherapy [22].

Neoadjuvant aromatase inhibitor study was performed in 239 postmenopausal women with hormone receptor-positive breast cancer, approximately one half of whom had LABC. In this trial, patients randomized to neoadjuvant aromatase inhibitor therapy (anastrozole or exemestan) or chemotherapy (doxorubicin plus paclitaxel) [23]. According to the results of the study, there was no difference for clinical response, pCR and disease progression between two groups. Therefore, in neoadjuvant setting for LABC, the optimal use of endocrine therapy seems to be best-suited for patients who are older or have comorbidities.

FUTURE DIRECTIONS

Ongoing clinical trials are now under way to evaluate the use of novel targeted agents in the neoadjuvant treatment of LABC. Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR) protein, is being added to a neoadjuvant cisplatin plus paclitaxel chemotherapy regimen in a phase II randomized trial in patients with triple-negative LABC. Many studies are investigating the anti-angiogenic agent bevacizumab combined chemotherapy in the setting of LABC. The primary endpoint of these trials is pCR.

CONFLICT OF INTEREST

There is no conflict of interest.

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