EDITORIAL

Escalating de-escalation in breast cancer treatment

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Abstract
Efforts have continually been made to de-escalate treatment for breast cancer, with the goal of balancing oncologic outcomes with complications and patient quality of life. In the early 2000s, two landmark studies firmly established that conservative treatment approaches for breast cancer can be safe and effective. More recently, neoadjuvant chemotherapy has gained momentum as a potential standard of care for breast cancer. An important question has thus arisen: Can neoadjuvant approaches themselves be de-escalated to further minimize adverse treatment effects while maintaining oncological outcomes? In this editorial, we look at the available evidence and assess current trends in treatment de-escalation for women with breast cancer.

Keywords Breast cancer · Surgical de-escalation · Multimodality therapy · Preoperative MRI · Upfront surgery · Neoadjuvant chemotherapy

Introduction

Beginning with the shift away from the Halstedian approach to breast cancer treatment [1], which was based on the concept that more surgery equals better control of disease, there has been a progressive movement toward de-escalation of treatment. Level 1 evidence from two clinical trials published in 2002 established that conservative approaches to breast cancer treatment are safe [2, 3]. These trials advanced the concept of multimodality treatment with integrated therapies for breast cancer.

The first integrated therapy approach to gain widespread acceptance for breast cancer was radiation therapy. Radiation therapy at the time, in the seventies, consisted of cobalt therapy and was associated with complications and late sequela [4], leaning the balance more toward risks than benefits in the de-escalation of surgery. In the 1970s, Bonadonna et al. established the advantages of cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy [5], ushering in

the era of systemic treatments with progressive escalation. During this time, anthracycline-based and/or taxane-based regimens, which resulted in a substantial survival benefit although at the cost of additional toxicity, were widely adopted [6, 7]. Recently, more-targeted therapies—including antihuman epidermal growth factor receptor 2 (HER2) agents, CDK4/6 inhibitors, Parp inhibitors, and immune checkpoint inhibitors—have gained acceptance, enriching and enhancing the integrated therapy options available for advanced and early-stage breast cancer [8–10]. Increasingly, breast cancer is understood to be a complex disease involving a wide variety of pathways and molecules, which helps explain the many challenges encountered when treating this disease [11].

At present, efforts to further de-escalate breast cancer treatment aim to combine these integrated therapies in a way that achieves optimal outcomes while avoiding both overtreatment and undertreatment. In this regard, personalized oncologic treatment is based on the careful selection of patients for the most appropriate treatment strategy. Genetics, genomics, and the development of mathematical tools such as nomograms are helping physicians to more optimally sequence treatments and identify approaches that result in better outcomes, better quality of life, and less toxicity for their patients. Genetics can help determine whether more investment in surgery is needed to decrease the risk of a second cancer [12]; genomics can help determine whether

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more hormonal therapy, as opposed to more chemotherapy, is needed, even for patients with stage II cancer [13]; mathematical tools such as nomograms can improve predictions of the efficacy of radiation therapy after conservation surgery for ductal carcinoma in situ [14]; and additional predictive tools can help make treatment choices for patients with breast cancer more scientific and less empiric.

Neoadjuvant and adjuvant chemotherapy

The modern approach to neoadjuvant chemotherapy allows for downstaging of cancer and de-escalation of breast and axillary surgery. The rate of pathologic complete response depends on the histologic type of the cancer, with maximal response in triple-negative and HER2-positive cancers. The exceptional rate of pathologic complete response that can be obtained after neoadjuvant chemotherapy in these cancers led to the exciting possibility of total de-escalation of surgery or avoidance of radiation therapy with ongoing trials [15]. However, the so-called less-responsive breast cancers—luminal cancers—can have a not negligible response rate (in up to 29% of patients), leading to the avoidance of axillary dissection in patients with luminal N1-positive cancers [16]. Predicting response to treatment for luminal cancers can be achieved by risk stratification using gene expression assays [17] or the less-expensive Ki-67 proliferation index.

Recent studies have shown that patients with an incomplete response to neoadjuvant treatment may benefit from adjuvant therapy, thus improving outcomes in these patients [18, 19]. The observed benefit in overall survival has led to a preference for neoadjuvant chemotherapy, instead of upfront surgery, for patients with triple-negative and HER2-positive breast cancer, including those with early-stage disease.

In this environment of continual improvement, an interesting question has arisen: In the microsphere of systemic treatment, is there a role for de-escalation of systemic neoadjuvant therapies? In recent years, numerous attempts have been made to de-escalate medical therapy in selected patients. HER2 blockers are so powerful that, in all likelihood, patients treated with these agents may need less chemotherapy to achieve the same effect. The trend in the early-stage setting is to limit the use of anthracycline as much as possible, given the increased risk of cardiotoxicity associated with its use. The TRAIN2 trial [20] observed equivalent pathologic complete response rates (approximately 70%) for paclitaxel, carboplatin, trastuzumab, and pertuzumab and anthracycline-based therapy (the standard of care), with similar survival outcomes. In the COMPASS-HER2 single-arm trial, patients with breast cancer (HER-2positive, stage II-IIIa, no disease after preoperative chemotherapy and HER2-targeted therapy) are being treated with

paclitaxel, trastuzumab, and pertuzumab; results from this trial are pending [21].

The Adjuvant Paclitaxel and Trastuzumab single-arm trial [22] was designed to investigate de-escalation of adjuvant therapy for HER2-positive early-stage breast cancer. The study included 410 patients with early-stage breast cancer (HER2positive, tumor < 3 cm, pN0) who received adjuvant paclitaxel and trastuzumab instead of standard treatment (doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab). Outcomes in this trial were comparable with outcomes in historical trials that included more-aggressive treatment. The incidence of side effects and quality of life were better with this dual-agent approach, and 3-year disease-free survival was 98.7% [22]. Most tumors were T1; only 36 were T2 (2.1–3.0 cm).

It remains to be determined whether a dual-agent therapy approach can be used in the neoadjuvant setting for small tumors. For instance, in light of the established efficacy of adjuvant treatment for patients without a response to neoadjuvant therapy, could a lesstoxic systemic approach such as paclitaxel and trastuzumab be effective in the neoadjuvant setting? The 2021 National Comprehensive Cancer Network guidelines and the 2019 St. Gallen Consensus Panel endorsed the use of preoperative systemic therapy in patients with ≥ T2 and/or ≥ N1 HER2-positive breast cancer, whereas primary upfront surgery is still recommended for patients with clinically node-negative (cN0) tumors ≤ 1 cm [6, 23]. Treatment for node-negative tumors measuring between > 1 and 2 cm (T1c) remains a gray area, however, with neoadjuvant chemotherapy and upfront surgery both acceptable approaches. Building on the multiple examples of successful de-escalation in the literature, some oncologists have begun to treat select patients with HER2-positive disease with adjuvant trastuzumab as monotherapy [24].

Clinical staging of breast cancer

The reliability of clinical staging, compared with final pathological staging, for patients with HER2-positive breast cancer remains an open question. HER2 invasive cancers are often associated with an extensive intraductal component [25], resulting in overstaging of the cancer by mammography and MRI. Diffuse microcalcifications can be seen on mammography, which correspond to the extensive intraductal component observed with large MRI enhancements. The invasive component of these cancers is often minimal, and the final pathological stage is often stage I.

The potential of MRI to overestimate disease is well known. Preoperative MRI has been shown to increase the use of more-aggressive treatment approaches, thus undermining attempts to de-escalate treatment without achieving a benefit in risk of local recurrence or disease-free survival [26–28]. Radiation therapy can eradicate possible

multicentric minimal disease not detected by conventional mammography or ultrasound, although this has not been shown to have an effect on rates of local recurrence. To its benefit, MRI, which is part of the routine management for patients receiving neoadjuvant chemotherapy, is the best means for assessing response to neoadjuvant chemotherapy [29]. Ultrasound remains an effective choice for screening dense breasts and plays a role in the differential diagnosis of breast lesions. Combined screening with mammography and ultrasound can detect 4.2 additional cancers per 1000 women, compared with mammography alone [29]. In a recent meta-analysis, ultrasound increased the effectiveness of multimodality diagnoses, with a pooled sensitivity of 80.1% (95% confidence interval [CI], 72.2%-86.3%), specificity of 88.4% (95% CI, 79.5%-93.6%), positive predictive value of 0.86 (95% CI, 0.81–0.91), and negative predictive value of 0.80 (95% CI, 0.75–0.85) [30]. Recently, the effectiveness of imaging modalities was shown to differ by subtype of breast cancer [31].

In a recent article in *Breast Cancer Research and Treatment* [32], ultrasound was shown to have the highest concordance with pathologic staging for HER2-positive cancer. Mammography and MRI resulted in overstaging. Unfortunately, only patients with stage I disease were considered in this study (patients with HER2-positive cancer are usually treated with neoadjuvant chemotherapy). Whereas ultrasound had the best concordance, MRI had the worst. A possible explanation for this is the ability of ultrasound to detect the solid component of the tumor, which is associated with the invasive component forming the mass [33]. An important point to consider is how many patients with T2-3N0 HER2-positive disease are overtreated with standard neoadjuvant chemotherapy (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, and now pertuzumab), considering that these cancers may be truly stage I but overstaged by mammography and ultrasound.

Selecting patients for anti-HER2 therapy

Does the omission of neoadjuvant chemotherapy and surgery upfront in patients with stage I HER2-positive cancers result in less-effective treatment? In cases of residual disease, regardless of initial clinical stage, patients are eligible for escalated adjuvant therapy with T-DM1, which provides a survival benefit over adjuvant trastuzumab, according to the KATHERINE trial [18]. This trial was designed for high-risk patients; patients with clinical stage I disease were underrepresented in the study population. As a result, it is difficult to quantify the benefit associated with T-DM1 in the subset of patients with stage I HER2-positive breast cancer who do not have pathologic complete response after neoadjuvant chemotherapy.

A typical scenario faced by a multidisciplinary breast team is a case of diffuse microcalcification requiring mastectomy, with core biopsies showing HER2-positive invasive ductal cancer and ductal carcinoma in situ and N0 disease. Should the medical oncology team start neoadjuvant chemotherapy, and, if yes, what type of chemotherapy? Or should the surgeon perform mastectomy, sentinel lymph node biopsy, or a possible axillary dissection, and is adjuvant chemotherapy without anthracycline indicated if the cancer is confirmed to be stage I? In other words, if we start neoadjuvant chemotherapy upfront, we may overtreat the patient, but we would have the benefit of assessing the pathologic response. If, on the other hand, we perform surgery first, we may de-escalate chemotherapy, but at the cost of forgoing information on pathologic response.

Axillary dissection

The incidence of pathologic axillary involvement in clinical T1N0 HER2-positive breast cancer is estimated to be 17.3%, making HER2 positivity a risk factor for lymph node involvement in some studies [34]. Unfortunately, the use of F-fluorodeoxyglucose positron emission tomography and computed tomography, which has a pooled sensitivity of 52%, does not help to better define axillary status [35]. Comparatively, ultrasound and fine-needle aspiration have a high specificity (0.97 [95% CI, 0.92–0.99]), and only 2.7% of patients with normal axillary findings on ultrasound were found to have > 2 metastatic nodes [36]. Axillary dissection is still the treatment of choice for mastectomy patients with sentinel node involvement and for breast-conservation patients with > 2 metastatic nodes; however, the alternative of radiation therapy is increasingly considered for patients with low nodal burden, as demonstrated in the AMAROS European trial [37–39]. Among patients with clinically occult pN1 breast cancer, neoadjuvant chemotherapy results in downstaging in 70% of those with triple-positive disease and 97% of those with estrogen receptor–negative/progesterone receptor–negative/HER2-positive disease, thus allowing for the avoidance of axillary dissection and, possibly, radiation, if it is not indicated by the characteristics of the primary tumor [16].

Pilewskie et al. reported on the likelihood of undergoing axillary dissection among patients with clinically N0 disease on the basis of treatment strategy. Among women with HER2-positive cancer, fewer women who received neoadjuvant chemotherapy required axillary lymph node dissection, compared with women who received upfront mastectomy (odds ratio, 0.19, $p = 0.001$). Conversely, for luminal cancers, the likelihood of axillary lymph node dissection was not significantly different between women who underwent neoadjuvant chemotherapy, upfront mastectomy, or breast-conserving surgery [40].

In balancing the risks and benefits of axillary dissection, we also need to consider the results of a recent cohort study that identified neoadjuvant chemotherapy as a risk factor for the development of lymphedema after axillary dissection. It is speculated that increased fibrosis and chronic inflammation—potential underlying mechanisms of lymphedema—may be less intense if chemotherapy is administered after surgery [41]. However, this interesting possibility remains to be confirmed. In considering the risk of lymphedema, clinical trials are in progress to assess the safety of avoiding radiation therapy after a complete response to neoadjuvant chemotherapy (NSABP B-51 RTOG 1304 [42]).

Conclusion

The results discussed above, which clearly show that neoadjuvant chemotherapy is associated with a survival benefit among non-responders and with downstaging of possible occult axillary disease, support the use of neoadjuvant chemotherapy in patients with T1 breast cancer who are candidates for mastectomy; however, which chemotherapy option is optimal remains a matter of debate.

Recent U.S. and European recommendations for treating HER2-positive breast cancer continue to advise upfront surgery for T1N0 breast cancers—for example, the American Society of Clinical Oncology recommends upfront surgery for patients with T1 tumors < 1 cm [43]. However, the definition of T1 is not cancer type specific, and the recommended treatment for T1 tumors involves clinical workup, mammography, ultrasound, and potentially, at the discretion of the treating physician, MRI.

Owing to the specificity of ultrasound for HER2-positive breast cancer and the predictive value of axillary ultrasound with fine-needle aspiration of suspicious nodes, the probability of migration of stage on final pathology for patients with T1N0 HER2-positive breast cancer should be considered very low. Furthermore, less-toxic neoadjuvant chemotherapy consisting of paclitaxel for 12 weeks plus 18 cycles of trastuzumab may be considered for these patients, as this approach includes a very low risk of undertreatment.

A possible strategy would be to perform sentinel node staging upfront and to use the information gained on response to neoadjuvant chemotherapy to inform further treatment for the primary breast cancer. A finding of a negative sentinel node in this setting would allow for the use of a less-toxic chemotherapy regimen. A limitation of this approach is the high false-negative rate of a second sentinel node mapping, after neoadjuvant chemotherapy, in patients with a positive sentinel node biopsy before neoadjuvant therapy, compromising the effectiveness of a second sentinel node biopsy to avoid axillary dissection [44].

Another possible clinical option would be to base clinical staging of the cancer on the results of the primary tumor ultrasound, the expression of the solid invasive component of the cancer, and the results of the axillary ultrasound for staging of the axilla. The medical oncologist could then begin a neoadjuvant approach with a less-aggressive chemotherapy regimen in cases of clinical stage I breast cancer. We believe that the chances of stage migration in cases of upfront surgery would be negligible, making the possibility of undertreatment with neoadjuvant chemotherapy very low.

Together with our article on clinical overstaging of breast cancer [29], and particularly in the setting of triple-positive breast cancer, we would like to send a message to the oncological community to take overstaging into account when evaluating patients for upfront surgery versus neoadjuvant chemotherapy. Identifying the solid component (the most representative of the invasive components) with ultrasound may better define the local stage of disease in these patients.

Declarations

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