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Controversies Concerning the Use of Neoadjuvant Systemic Therapy for Primary Breast Cancer

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Abstract The major aim of neoadjuvant systemic therapy is to improve prognosis by individualizing treatment. The proven benefits of neoadjuvant systemic therapy include reducing tumor burden, higher breast-conserving surgery, and the possibility of in vivo monitoring of response to treatment. Other goals of neoadjuvant treatment are the detection of new prognostic and predictive biomarkers and the investigation of new drugs and imaging modalities. Although many prospective trials have answered important questions regarding neoadjuvant systemic therapy, several topics remain controversial.

Introduction

Breast cancer is the most frequent cancer in women worldwide. Even though the incidence of malignant breast tumors has increased, improvement in treatment has led to a decrease of mortality over the last two decades [1]. Nevertheless, mortality rates increase with inclining stage of disease [2]. Especially for locally advanced breast cancer, efforts have been made to downstage disease to improve the prognosis using neoadjuvant systemic treatment (NAST). The major aim of NAST is to improve prognosis by individualizing treatment. In addition to reducing the tumor burden, the proven benefits of NAST include higher rates of breast-conserving surgery and the possibility of in vivo monitoring of the response to treatment. Other proposed goals are detection of new prognostic and predictive biomarkers and the investigation of new drugs and imaging modalities. Although many prospective trials have answered important questions regarding NAST, several topics remain controversial, which are addressed in the following sections. They include the following.

- General noninferiority of neoadjuvant to adjuvant systemic treatment
- Selection criteria for the best candidates for NAST
- Optimal initial staging
- Choice and length of systemic treatment
- Optimal response monitoring
- Surgery after NAST
- Adjuvant radiotherapy
- Postsurgical systemic treatment
- Best surrogate markers for prognosis

Noninferiority of neoadjuvant compared to adjuvant treatment

Whereas an increase in the breast conservation rate and a reduction in the surgical extent for large tumors are proven benefits, some controversy still exists on the equivalence of NAST compared to adjuvant treatment regarding progression-free and overall survivals. Various major Phase III trials have demonstrated the equivalence of neoadjuvant and adjuvant treatment in terms of progression-free and overall survivals. In an earlier meta-analysis [3], the authors observed no differences in disease-free survival, distant metastasis-free survival, and overall survival but a higher risk for locoregional recurrences for those neoadjuvant-treated patients who chose radiotherapy without surgery. In a more recent meta-analysis (D. Mauri, personal communication, 2010) no differences were observed in the

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risk of death [relative risk (RR) 0.99, 95% confidence interval (CI) 0.92–1.07], the risk of recurrence (RR 0.99, 95% CI 0.95–1.05), or risk of distant recurrence (RR 0.98, 95% CI 0.90–1.06). This indicates that NAST is at least as safe as adjuvant treatment. Supporters of NAST point out that the opportunity of adjusting therapy in cases of progressive disease and the opportunity of down-staging the axilla might lead to a better prognosis for women treated prior to surgery.

Selection criteria for the best candidates for NAST including prognostic and predictive markers

Although NAST represents the standard of care for inflammatory breast cancer [4], the selection criteria for candidates for NAST in contrast to adjuvant treatment are controversial. Generally, any patient who is a candidate for adjuvant systemic chemotherapy can be considered for neoadjuvant systemic chemotherapy. Patients with inoperable, locally advanced breast cancer or large breast tumors (>2 cm) and proven nodal involvement are optimal candidates. Factors such as triple negativity, high-grade cancer and a high proliferative rate in estrogen receptor (ER)-positive disease, and Her2 positivity are predictive of high pathology complete response (pCR) rates. Consequently, patients whose tumors meet those criteria should also be chosen for the neoadjuvant approach [5]. Treatment of small tumors (<2 cm) with neoadjuvant systemic chemotherapy could contain a possible risk of overtreatment because the primary surgery and diligent pathology assessment could detect candidates with very small tumor size where chemotherapy might be avoided. Additionally, it is not clear whether cytologically or histologically confirmed nodal involvement alone has sufficient weight regarding the choice of applying NAST. Thus, this subject needs further investigation. Also, some opponents of neoadjuvant treatment argue that patients with extensive nodal involvement profit more from dose-dense chemotherapy. In contrast, small tumors that are of low to intermediate grade, ER-positive, and/or Her2-negative with lobular histology and a low or intermediate proliferation rate seem not to benefit from neoadjuvant chemotherapy. Those patients are possible candidates for neoadjuvant endocrine treatment, especially those with severe co-morbidities.

Optimal initial staging

The basis for an optimal treatment recommendation and patient counseling are a detailed physical examination of the breast and nodal areas, ultrasonography (US), and mammography. In certain cases (lobular or multicentric carcinoma, dense breast, *BRCA1* and *BRCA2* mutation carriers), magnetic resonance imaging (MRI) provides additional diagnostic information but remains controversial. US or MRI may be appropriate methods to assess the lymph node status, depending on local expertise and access to imaging modalities. Additional cytologic or histologic evaluation of the nodes can be provided by fine-needle aspiration or core cut biopsy. A standardized photograph of the size and location of the tumor can help locate the initial extent in cases of a complete remission [6]. All suspicious lesions and, if possible, nodes should be histologically confirmed by core cut biopsy. This includes a minimum of two or three cuts to document the cancer. Ideally, additional tissue should be banked for research or future translational questions. The pathology results should contain the histologic subtype of cancer, grade, proliferation index (e.g., Ki67 level), and ER, progesterone receptor, and Her2 status determined with methods recommended by American Society of Clinical Oncology/College of American Pathologists guidelines [7, 8]. There is not yet consistency about the need to determine receptor status and the grade of coexisting ductal carcinoma in situ (DCIS).

Choice and length of NAST (endocrine/chemotherapy ± targeted therapy)

After the deciding to apply NAST, the next step to choose between neoadjuvant systemic endocrine treatment or cytotoxic chemotherapy (NSCT). In the case of NSCT, sequential or concurrent combination of anthracyclines and taxanes are the most extensively evaluated and comprise most effective third-generation adjuvant/neoadjuvant chemotherapy regimens. Thus, an NSCT regimen, used outside a clinical trial, should include concurrently or sequentially used anthracyclines and taxanes for at least six cycles (concurrent regimens) or 6 months (as sequential regimens). So far, there has been no direct comparison between sequential and concurrent regimens. Some trial data exist for splitting chemotherapy into preoperative and postoperative parts. The advantages of complete preoperative administration are an improvement in neoadjuvant response rates and higher compliance. Also, discontinuation of the chemotherapy course by surgical treatment may negatively influence the long-term efficacy of the treatment by allowing regrowth of micrometastatic lesions. However, whether sandwiched preoperative and postoperative chemotherapy is indeed inferior to administering all of the NSCT before surgery has not been extensively studied in adequately powered clinical trials and hence remains a theoretical concern. Analogous to the adjuvant approach, dose-dense trials demonstrated higher response rates than conventional dosing. However, further investigations are

needed using recent standard regimens as the control arm [9].

All patients with HER2-overexpressing tumors—except those with cardiac co-morbidities—should be treated with trastuzumab. Adjuvant trials demonstrated that cardiotoxicity is not increased if trastuzumab is given concurrently with taxanes. Published data based on a relatively small number of highly selected patients suggests that trastuzumab can be safely administered concurrently with epirubicin-based regimens (with an attenuated epirubicin dose of 75 mg/m^2) for four cycles followed by concurrent trastuzumab and a taxane in patients without cardiac co-morbidity. This combination is a highly effective regimen that produces pCR rates close to or >50% [10, 11]. Such a regimen represents an option for younger woman with normal cardiac function who are at high risk for recurrence. Patients must be monitored and informed about the potential of cardiac toxicity and the current contraindication of using trastuzumab in combination with an anthracycline [12–14]. Possible improvements in new anthracycline formulations (e.g., pegylated liposomal doxorubicin) need to be investigated. Following the promising results of the NEO-ALTTO [15] and NEOSPHERE [16] studies, some patients may be selected to receive a combination of two Her2-targeted therapies alone.

Retrospective data suggest that *BRCA1* and *BRCA2* patients are at least as likely and may be even more likely to have sporadic breast cancer that responds to current standard anthracycline/taxane-based NSCT [17]. Although platinum salts and poly ADP ribose polymerase (PARP) inhibitors provided promising results as active agents in mutation carriers [18–21], they should so far be prescribed only in clinical trials.

Breast cancer patients diagnosed after the first trimester of pregnancy, when treated with NAST, should receive the same chemotherapy regimens as nonpregnant women, except for antimetabolites and newer targeted agents (bevacizumab, PARP inhibitors) because of the limited toxicity data on those agents regarding their effect on the fetus [22]. Available data for trastuzumab suggest that its use after the first trimester seems not to affect the fetus and pregnancy.

Neoadjuvant systemic endocrine treatment is an alternative treatment, particularly for postmenopausal patients with ER-positive cancers [23] or older patients with co-morbidities, whose general condition disallows chemotherapy or even surgery. Aromatase inhibitors given for at least 4 months are generally the agents of choice [24–28]. Based on trials conducted in a metastatic setting [29], a combination of endocrine therapy with Her2-targeted therapy earned further validation. Young patients with low ER expression, high Ki67 levels, or HER2-positive cancers should not be chosen for endocrine-based neoadjuvant treatment outside a trial.

Optimal treatment monitoring modalities and intervals in NST

Another controversial topic is optimal treatment monitoring during NAST. It is widely accepted that monitoring must include clinical examination of the breast and nodes before each cycle. Many NAST trials included mammographic and sonographic evaluation. Those imaging modalities are easy to use, generally available, and provide good reproducibility and specificity. Furthermore, US provides the opportunity to clip the tumor bed in cases of complete remission. So far there is no clear evidence regarding the optimum intervals between imaging assessments. Some data exist on treatment monitoring with MRI, spectroscopy, and positron emission tomography scans [30]. The use of those modalities provides better sensitivity and specificity in difficult cases (e.g., inflammatory breast cancer, lobular carcinoma, multifocality and multicentricity, young women with dense breasts) and allows metabolic assessment of the tumors. Further investigation must clarify the value of the widely used US and mammography and the indications for additional modalities.

Best surgical approach for each neoadjuvant-treated case

Currently, surgical therapy is needed in every case and should be done by an experienced and dedicated breast surgeon. If possible, breast-conserving surgery (BCS) should be done with clearly negative margins for invasive cancer and DCIS. Preoperative marking of the tumor with US, mammography, MRI, or a clip can help surgeons identify the previous tumor region in cases of a complete response. Specimen radiography is frequently helpful intraoperatively for assessing the margins in BCS cases. The value of intraoperative fresh frozen sections for assessing margins is not validated. Similar to sporadic breast cancer, *BRCA* mutation carriers who demonstrate partial or complete response to NSCT can undergo BCS. In those patients, BCS and radiotherapy has resulted in rates of local recurrence in the same quadrant that are similar to those observed with sporadic breast cancer. However, the long-term risks of second primary breast cancers in either breast are significantly higher in *BRCA* carriers [17, 31]. Because initial diagnosis and therapy monitoring is difficult for pure lobular cancers, with multicentricity often occurring, surgery should be undertaken based on the initial extent of the primary tumor in those cases. Patients with inflammatory breast cancer or planned prophylactic contralateral mastectomy, those with persistent positive margins after repeat margin resection, multicentric lesions (more than two lesions in different quadrants), and patients

with widespread DCIS or microcalcifications should undergo mastectomy with secondary reconstruction as postoperative radiotherapy is presumed. In general, breast reconstruction should follow the same rules as those for primary surgery.

Sentinel lymph node biopsy (SLNB) should only be considered for patients who have clinically negative lymph nodes (including on imaging the axilla at the time of diagnosis). However, one of the most controversial topics is the timing of SLNB in conjunction with NSCT [32]. A negative SLNB before NSCT generally eliminates the need for axillary lymph node dissection without the confounding effects of NSCT. Moreover, NSCT might negatively influence lymphatic mapping through fibrosis and obstruction of lymph vessels. Initial histologic nodal staging is also preferred by some radiotherapists because their recommended treatment is based on the initial pathologic stage. This staging could also be accomplished by high-quality US or MRI evaluation and image-guided fine-needle aspiration (FNA) of any suspicious nodes. On the other hand, if a positive sentinel node is removed by SLNB before NSCT, the degree of remission in the axilla after NSCT cannot be assessed accurately. It has been proposed that when SLNB is performed after NSCT the extent of axillary surgery can be reduced because NSCT converted positive lymph nodes to negative nodes in 20–40% of the cases [33]. Down-staging of the axilla seems to be the best prognostic factor. However, so far no conclusive data exist about the recurrence rates in initially node-positive disease that becomes node-negative by NSCT.

In conclusion, SLNB should be performed after NSCT only in patients whose axilla is clinically negative by US or MRI or by FNA (core cut biopsy). Until data from further trials are available, full axillary lymph node dissection is recommended following NSCT in patients with biopsy-confirmed axillary lymph node involvement prior to NSCT. Ongoing prospective clinical trials that will clarify many of the issues concerning SNB in the context of NSCT are the SENTINA substudy of the GEPARQUINTO trial [34] and the ACOSOG-1071 trial [35]. Importantly, these points refer only to patients with large operable breast cancer and should not be extrapolated to those with locally advanced disease, including patients with inflammatory breast cancer because the accuracy of SNB after NST has not been convincingly demonstrated in these groups of patients. For such cases, conventional axillary dissection is recommended.

Optimal adjuvant radiotherapy after NST

The decision to apply radiotherapy after neoadjuvant therapy must take into consideration whether BCS or mastectomy is performed. At present, all patients with BCS require radiotherapy. Predictive factors that help to choose patients in whom radiotherapy can be omitted after BCS must be detected by future trials. The role of intraoperative irradiation or postoperative irradiation with hypofractionated protocols for patients who have undergone BCS has to be investigated and validated. Not as clear is the need for radiotherapy after mastectomy. Data from the NSABP regarding postmastectomy irradiation are still under evaluation [36]. In general, radiotherapy recommendations should be guided by the initial clinical stage (tumor size and nodal involvement) and by the pathology findings after surgery. Radiotherapy after mastectomy is indicated in all patients but especially for young women with at least one positive lymph node after NSCT and in those with locally advanced or inflammatory breast cancer regardless of their response to NSCT [37]. Uncertainty exists about the need for postmastectomy irradiation in patients with only micrometastases at the initial staging. Additional studies are also needed to define the role of radiotherapy after mastectomy in node-negative patients with various extents of residual disease in the breast after NSCT.

Choice and length of postsurgical systemic treatment

In addition to radiotherapy, postsurgical medical treatment is based on adjuvant recommendations. There are no trial data demonstrating a benefit of additional adjuvant chemotherapy after completion of a full course (4–6 months) of anthracycline/taxane-based NSCT—either in general or for patients who have extensive residual cancer. All patients with hormone receptor-positive breast cancers should receive endocrine treatment. Patients with Her2 positivity should be given trastuzumab for 1 year. No data suggest an additional benefit of a longer duration of endocrine therapy or treatment with trastuzumab. Also, the benefit from adjuvant use of bisphosphonates [38–40] is controversial and should be addressed in additional randomized trials.

Which factors can be used as surrogate markers for prognosis

Currently, the pCR rate is one of the most important efficacy endpoints. pCR was shown to correlate with a favorable prognosis in most trials. Nevertheless, only 30–60% of patients reach this endpoint, and recurrence rates vary in this cohort, suggesting that there might be other prognostic factors (e.g., for neoadjuvant endocrine treatment) that have to be detected and validated in future trials. Not only new prognostic but also predictive factors that are specific for certain drugs or regimens are needed

and should be identified to allow greater individualization of treatment for each patient.

Conclusions

Today, NAST represents a milestone in breast cancer therapy and research. At present, it is comparable to adjuvant systemic treatment with regard to prognosis. However, it has several advantages: in vivo testing of the response to a drug(s), a reduction in the extent of surgery, an increase in the performance of BCS, and multiple possibilities for translational research and the development of new anticancer drugs. Current controversies include identification of the best candidates for NAST, optimal modalities of treatment monitoring, choice of drugs, and several points regarding surgery (SLNB, mastectomy), radiotherapy (locoregional, postmastectomy), and postsurgical treatment. To address these controversial questions, further clinical, translational, and molecular research in the field of neoadjuvant treatment of breast cancer is needed.

Conflict of interest The authors declare no conflicts of interest.

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