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Trends and Novel Approaches in Neoadjuvant Treatment of Breast Cancer

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Keywords
Breast cancer · Chemotherapy · Neoadjuvant therapy · Targeted therapy

Summary
Breast cancer is the most prevalent malignant disease in women worldwide. Traditionally, surgical tumour resection was the primary step within the treatment algorithm of early stage disease; systemic therapy in order to reduce the rate of systemic recurrences followed. National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-18 found that pre- and postoperative administration of chemotherapy was equally effective. This study therefore established neoadjuvant chemotherapy as a valid treatment option, as the breast conservation rate is increased. Modern neoadjuvant regimens encompassing anthracyclines and taxanes yield pathological complete response (pCR) rates of around 20%, with higher efficacy observed in triple-negative tumours. The antibody trastuzumab is the first targeted agent established in neoadjuvant regimens for the treatment of Her2-positive breast cancer, as it raised pCR rates up to 50%. Novel approaches are aiming to increase the efficacy of neoadjuvant therapy. Inclusion of capecitabine might further increase pCR rates in selected patients, although data are not unanimous throughout the respective clinical trials. In patients harbouring BRCA-1 germline mutations, platinum derivatives are apparently promising. Novel Her2-targeted agents such as lapatinib and pertuzumab are currently under investigation in several clinical trials, while the role of bevacizumab, a monoclonal antibody inhibiting angiogenesis, awaits future clarification.

Schlüsselwörter
Brustkrebs · Chemotherapie · Neoadjuvante Therapie · Zielgerichtete Therapie

Zusammenfassung
Brustkrebs ist der häufigste bösartige Tumor bei Frauen. Traditionell stellt die Operation den ersten Behandlungsschritt dar, eine systemische Therapie wird meist danach verabreicht. Die Studie B-18 der NSABP (National Surgical Adjuvant Breast and Bowel Project) konnte nachweisen, dass kein Nachteil resultiert, wenn die systemische Therapie vor einer Operation verabreicht wird. Als Vorteil zeigte sich eine signifikant höhere Rate an brusterhaltenden Operationen. Moderne neoadjuvante Regime enthalten Anthrazykline und Taxane, wodurch ein pathologisch komplettes Ansprechen (pCR) bei etwa 20% der Patientinnen erzielt wird. Bei tripel-negativen Tumoren wurde eine überlegene Wirksamkeit beobachtet. Mit pCR-Raten von bis zu 50% ist Trastuzumab, ein gegen den Her2-Rezeptor gerichteter monoklonaler Antikörper, die erste zielgerichtete Therapie, die Eingang in die neoadjuvante Behandlung Her2-positiver Tumore gefunden hat. Bei einem Teil der Patientinnen scheint eine Erweiterung der Chemotherapie um zusätzliche Zytostatika wie Capecitabin die pCR-Raten zu steigern, allerdings sind die diesbezüglichen Ergebnisse klinischer Studien nicht einhellig. Bei Frauen mit erblicher BRCA-1-Mutation könnten Platinderivate eine besondere Wirksamkeit aufweisen. Bei Her2-positiven Tumoren werden alternativ oder additiv zu Trastuzumab Substanzen wie Lapatinib und Pertuzumab in klinischen Studien getestet, bislang vorliegende Ergebnisse erscheinen vielversprechend. Die Rolle von Bevacizumab, einem Antikörper gegen den Gefäßwachstumsfaktor VEGF, im neoadjuvanten Setting ist unklar, und weitere Ergebnisse müssen abgewartet werden.

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Introduction

The term breast cancer as understood today summarizes a heterogeneous group of malignancies with major disparities in terms of prognosis and treatment response. The Stanford Group first established the classic 'intrinsic classification' of luminal, human epidermal growth factor receptor 2 (Her2)-positive, normal-like, and basal-like cancers [1]. Herein, luminal is once more separated into luminal A – highly oestrogen-dependent and therefore oestrogen receptor- and progesterone receptor-positive with low grading and a low proliferation rate – and a less endocrine-responsive subtype called luminal B. The Her2-positive subtype describes highly consistent Her2-positive cancers as defined by immunohistochemistry or fluorescence-in-situ-hybridization (FISH). Basal-like breast cancers have a gene expression profile similar to the profile of myoepithelial cells of the basal epithelial layer of milk ducts [1]. Typically, those tumours are characterized by the lack of Her2 as well as hormone receptor (HR) expression; therefore, in the clinical routine setting, the term 'triple-negative tumour' is often used as surrogate for the basal-like subtype, with approximately 80% concordance [2]. While targeted treatment options are available for HR-positive and Her2-positive tumours, chemotherapy remains the mainstay of treatment for triple-negative disease. It was recently suggested that so-called core basal-likes were related to tumours harbouring germline BRCA-1 mutations [3]. This, in terms, lead to the assumption that certain treatment strategies such as inhibitors of PARP-1 or platinum salts might prove fruitful in the treatment of triple-negative breast cancers [4].

Breast Cancer and Neoadjuvant Therapy

Starting in the 1970ies, preoperative systemic therapy was initially administered in cases of locally advanced inoperable breast cancer only [5]. Since those days, the concept of neoadjuvant treatment has evolved to become a standard in operable disease also, with the objective to increase the rate of breast conservation [6]. A milestone in this process was National Surgical Breast and Bowel Project (NSABP) trial B-18 which established equal efficacy of 4 cycles of doxorubicin plus cyclophosphamide, whether given before or after operation [7].

Over the last 30 years, a broad spectrum of different chemotherapeutic drugs has been studied in the neoadjuvant setting. Based upon those results, the respective consensus statements of the 2009 and 2011 St. Gallen Conferences state that neoadjuvant chemotherapy regimens should contain an anthracycline and a taxane [8, 9]; as for the duration of neoadjuvant chemotherapy, it appears that the rate of pathological complete response (pCR) is significantly higher when more than 3–4 cycles of therapy are administered [10].

Recently, targeted therapies such as trastuzumab, a monoclonal antibody targeting Her2, were introduced. Other drugs targeting Her2, such as the antibody pertuzumab and the tyrosine kinase inhibitor lapatinib, are currently evaluated in clinical trials [11, 12]. Bevacizumab, a monoclonal antibody binding the angiogenic growth factor VEGF (vascular endothelial growth factor), was also studied in clinical trials [13, 14], but its exact role in neoadjuvant treatment still remains elusive.

Besides the opportunity of increasing the rate of breast conservation, preoperative therapy offers the advantage of testing a tumour's chemosensitivity in vivo. On the downside, an increased rate of locoregional recurrences was suggested in a meta-analysis of neoadjuvant trials [15]. It is, however, important to remember that the mentioned meta-analysis included trials where operation was withheld in numerous patients of the respective neoadjuvant treatment groups. This assumption was strengthened by a positive test for interaction. Therefore, it is not proven that neoadjuvant treatment followed by optimal local therapy will increase the rate of locoregional recurrence.

Endpoints of Neoadjuvant Therapy

pCR, which indicates improved survival, is often regarded the most pertinent endpoint to assess the efficacy of neoadjuvant treatment [16–18]. Prognostic value of pCR was recently also established in Her2-positive disease [19]. Clearly, however, dichotomization of patients' response to neoadjuvant chemotherapy as pCR or no pCR is too simplistic. Prognosis of patients with residual disease still varies depending on the grade of response – from near pCR to complete resistance. Therefore, Symmans et al. [20] developed the residual cancer burden (RCB) score which incorporates pathologic measurements of primary tumour (size and cellularity) and nodal metastases (number and size). From today's view, the RCB score offers a meaningful alternative to pCR as primary endpoint in future trials of neoadjuvant chemotherapy.

Chemotherapy

Platinum Derivatives

Similar to tumours harbouring BRCA-1 germline mutations, core basal-like tumours apparently have deficient DNA repair pathways; it was therefore hypothesized that this subtype might be highly responsive to treatment with platinum salts. To test that assumption, trials were conducted in triple-negative tumours which encompass the majority of basal-like cancers. In metastatic breast cancer, progression-free survival in patients receiving platinum-based chemotherapy was significantly longer in the triple-negative group (6 vs. 4 months;

p = 0.05) [21]. In the preoperative setting, a pathologic complete remission rate of 62% (95% confidence interval (CI) 50–73%) was achieved with cisplatin/epirubicin/paclitaxel triplets in a population of 74 triple-negative patients [22]. The BALI-1 study, however, reported disappointing results: the response rate of first-line cisplatin in triple-negative tumours was 10%, far less than anticipated [23]. This clearly demonstrates that triple-negative receptor status alone is insufficient to serve as response predictor.

In contrast to those findings, BRCA-1 germ-line mutations may in fact predict for response to neoadjuvant platinum-based chemotherapy. A small single-arm phase II study of single-agent cisplatin as neoadjuvant treatment for patients with BRCA-1-mutated breast cancer reported an unprecedented pCR rate of 90% [24]. On the other hand, BRCA-1-mutated tumours were found to be relatively resistant to taxane-based chemotherapy [25]. Due to those intriguing data, randomized trials assessing the role of platinum salts in BRCA-1 carriers are warranted. While BRCA-1 mutations are rarely found in sporadic triple-negative cancers, BRCA-1 inactivation due to promoter methylation might occur in around 40% of patients [26]. This renders BRCA-1 promoter methylation an interesting biomarker for prediction of response to neoadjuvant chemotherapy.

Capecitabine

Recently, 2 large randomized trials reported results with capecitabine in the neoadjuvant setting. ABCSG-24, a trial by the Austrian Breast and Colorectal Cancer Study Group (ABCSG), showed that the addition of capecitabine to a standard epirubicine and docetaxel regimen resulted in a significantly higher rate of pCR of 24 versus 16% (p = 0.02) paralleled by an increased but manageable toxicity rate. A preplanned subgroup analysis of triple-negative tumours showed a very high pCR rate of 48% in the capecitabine arm as compared to only 13% in non-triple-negative tumours [27]. This is in good accordance with results of the Finnish adjuvant FinXX trial [28] in patients with moderate-to-high-risk early breast cancer where recurrence-free survival at 3 years follow-up was significantly better with the capecitabine regimen than in the standard control arm (93 vs. 89%; hazard ratio (HR) 0.66; 95% CI 0.47–0.94; p = 0.020). In an explorative analysis of this study, the triple-negative subgroup especially profited from capecitabine in terms of recurrence-free survival with a HR of 0.43 (p = 0.024) [29]. In contrast, the German GeparQuattro trial did not show an altered pCR rate when capecitabine was added to neoadjuvant docetaxel [30]. These differences in study results may be explained by the fact that the trial designs differed significantly since ABCSG-24 and the Finnish adjuvant trial administered 6 cycles of upfront capecitabine in a combination regimen, whereas in GeparQuattro only 4 cycles of capecitabine and docetaxel where given after an already highly effective anthracycline-containing induction therapy which also included cyclophosphamide. Moreover, triple-negative breast cancer appears to be a heterogenous subgroup in itself, which may also in part explain the differing study results. In summary, these results point to the fact that capecitabine may play a relevant role in the adjuvant and neoadjuvant treatment of breast cancer in general, and triple-negative tumours in particular [31]. To better define its role, further prospective evaluations are warranted.

Targeted Therapy

Her2-Directed Targeted Therapy

Her2 is a transmembrane receptor molecule of the Her family of human growth factor receptors. Her2 forms homo- or heterodimers with other proteins of the Her family; dimerization results in phosphorylation of tyrosine residues on the cytoplasmatic domain, which in terms activates downstream signalling pathways responsible for upregulation of cell proliferation, angiogenesis, and evasion of apoptosis [32].

Trastuzumab (rhMAb4D5) is a recombinant, humanized monoclonal antibody targeting the extra-cellular domain of Her2. Upon receptor binding, antibody-dependent cellular cytotoxicity and signalling inhibition causes cell degradation [33–35]. Trastuzumab is well established in palliative as well as adjuvant treatment of Her2-positive breast cancer. In the neoadjuvant setting, phase II studies incorporating trastuzumab reported pCR rates in the range of 18–39% [36–38]. In a randomized study, Budzar et al. [39] treated patients with 4 cycles of paclitaxel followed by 4 cycles of FEC (fluorouracil, epirubicin, cyclophosphamide) with or without weekly trastuzumab for 24 weeks. After the inclusion of only 42 patients, a significant difference in terms of pCR rate in favour of trastuzumab was observed, and the trial was terminated (66.7 vs. 25%; p = 0.02). Based upon those results, further studies were initiated. In 228 patients with locally advanced Her2-positive breast cancer treated with doxorubicin plus paclitaxel followed by paclitaxel and CMF (cyclophosphamide, methotrexate, fluorouracil) with or without trastuzumab, Gianni et al. [40] observed a pCR rate of 23% with chemotherapy alone; addition of trastuzumab increased this number to 43% (p = 0.002). The GeparQuattro conducted by the German Breast Group finally established the incorporation of trastuzumab into neoadjuvant therapy of early breast cancer. 445 patients were randomly assigned to 4 cycles of EC (epirubicin, cyclophosphamide) followed by 4 cycles of docetaxel (+/– capecitabine) with or without trastuzumab. pCR rate (defined as no invasive or in situ residual tumours in the breast) was 31.7% in the trastuzumab group compared to 15.7% in the reference group. Importantly, the short-term cardiac toxicity profile was comparable between the 2 arms [41].

Novel approaches in the neoadjuvant therapy of Her2-positive disease include the incorporation of other Her2-targeted agents as well as chemotherapy-free biological treatment concepts. In the Her2-positive population of the GeparQuinto study, patients were randomized to 4 × EC followed by 4 cycles of docetaxel in combination with trastuzumab or the tyrosine kinase inhibitor lapatinib. pCR rate, defined as no residual invasive tumour in the breast and the lymph nodes, was significantly higher in the trastuzumab arm (45 vs. 30%), further strengthening the role of trastuzumab in the neoadjuvant setting [42].

The NeoAltto trial randomly assigned 450 patients with operable breast cancer to 18 weeks of neoadjuvant targeted therapy with lapatinib, trastuzumab, or the combination of both drugs; each arm also contained 12 administrations of weekly paclitaxel. pCR rate was significantly higher in the combination arm (51.3%) compared to the respective single agent trastuzumab or lapatinib arms. Importantly, pCR rate was highest in HR-negative disease (61.3 vs. 41.6%), in line with data of neoadjuvant chemotherapy in triple-negative tumours. Toxicity, however, was increased by the addition of lapatinib, and around 65% of patients in both lapatinib-containing arms completed treatment as scheduled, compared to more than 90% in the trastuzumab group [11]. There is a strong biological rationale for the combination of trastuzumab and lapatinib, as lapatinib inhibits Her2 downregulation in response to antibody binding, thereby potentially increasing the efficacy of trastuzumab [43]. Still, as considerable toxicity was observed in the combination arm, and no established neoadjuvant regimen was used as chemotherapy backbone, a direct randomized comparison to the current standard of care is needed in order to fully assess the future role of lapatinib plus trastuzumab combinations in the neoadjuvant setting.

Finally, NeoSphere was a 4-arm phase II trial that randomly assigned patients to docetaxel plus trastuzumab, docetaxel plus pertuzumab, an alternative Her2-targeting antibody, and docetaxel plus the combination of both antibodies. A 4th arm consisted of trastuzumab and pertuzumab alone without a chemotherapy backbone. Total treatment duration was 12 weeks. While once again the triple-combination arm yielded highest pCR rates (46%), this study was the first to report a clinically meaningful activity of a chemotherapy-free combination regimen in the neoadjuvant setting with a pCR rate of 17% [12]. Again, those results clearly emphasize that dual Her2 receptor blockade is promising. As with NeoAltto, however, direct comparison to regimens with standard duration and a standard chemotherapy backbone is necessary.

Trastuzumab-DM 1 (T-DM 1) is another promising option for the treatment of Her2-positive breast cancers; this antibody plus chemotherapy conjugate consists of trastuzumab and DM 1, a derivative of the anti-microtubule agent maytansine [44]. The compound has proven activity in Her2-positive metastatic breast cancer and is currently under investigation in a phase III clinical trial comparing T-DM 1 to trastuzumab plus docetaxel or paclitaxel (MARIANNE; NCT01120184). Due to its favourable toxicity profile, T-DM 1 is another attractive option in the neoadjuvant setting. Her2-targeted vaccination strategies, on the other hand, might be more useful as adjuvant therapy of breast cancer patients [45].

VEGF-Directed Therapy

VEGF was identified as the most important driving force behind malignant angiogenesis [46]. Inhibition of VEGF or the VEGF receptor therefore appeared to be a promising treatment approach. While somewhat disputed, the monoclonal antibody bevacizumab was the first VEGF-targeted drug incorporated into the therapy of breast cancer. In metastatic breast cancer, data of 5 clinical trials have become available. 4 of those were positive, the only negative study was conducted in heavily pretreated patients [47–51]. Based upon those results, studies were initiated evaluating the role of bevacizumab in early stage breast cancer. NSABP B-40 was a prospective randomized neoadjuvant phase III trial utilizing 4 × AC (doxorubicin plus cyclophosphamide) followed by 4 cycles of docetaxel as chemotherapy backbone. The study asked 2 questions: First, will the addition of gemcitabine or capecitabine increase the efficacy of chemotherapy? Second, will the addition of bevacizumab yield additional benefit? While intensification of conventional chemotherapy did not improve pCR rates, a significantly higher pCR rate was observed in the bevacizumab arm (34.5 vs. 28.4%; $p = 0.027$). It is important to note that this benefit resulted solely from an increased pCR rate in HR-positive patients [14]. Results in the Her2-negative population of GeparQuinto, however, hint in the exact opposite direction. In the triple-negative subgroup, the addition of bevacizumab to standard chemotherapy yielded a significantly higher pCR rate, while no effect was observed in HR-positive patients [13]. Different sequencing of taxane and anthracyclines might be a potential reason; also, the duration of bevacizumab treatment differed between both studies. In general, however, the controversial results of NSABP B-40 and GeparTrio cannot be explained for now. Clearly, this once again highlights the urgent need to identify predictive markers for anti-angiogenic therapy in breast cancer.

ABCSG has recently started a randomized phase II study of a non-pegylated liposomale anthracycline in combination with docetaxel and trastuzumab with or without bevacizumab in Her2-positive patients (ABCSG-32, NCT01367028). There is a strong rationale for this combination, as Her2 signalling causes increased VEGF expression via the ras/raf/MAPKinase pathway [52] due to an increase in HIF-1α [53], a mechanism that may be blocked by trastuzumab. Indeed, Konecny et al. [54] suggested that the association between Her2 and VEGF expression points to VEGF as a relevant fac-

tor in the aggressiveness of the Her2-positive phenotype, and therefore supports the use of combination therapies directed against both Her2 and VEGF.

Invasive lobular cancer appears to derive less benefit from neoadjuvant chemotherapy, and neoadjuvant endocrine therapy may be a reasonable option for selected patients [6, 55]. Therefore, ABCSG-33 will evaluate the additive value of bevacizumab to neoadjuvant aromatase inhibitors in patients who are not candidates for neoadjuvant chemotherapy.

Cancer Vaccines and Chemotherapy Schedules

ABCSG-34 is the 3rd trial of ABCSG's new generation of neoadjuvant studies. ABCSG-34 asks the question whether the addition of the L-BLP25 liposome vaccine to neoadjuvant therapy improves upon the activity of conventional preoperative treatment of Her2-negative breast cancer patients. The vaccine has a synthetic lipopeptide sequence identical to a recurring sequence of the mucinous glycoprotein 1 (MUC-1) which is an integral cell membrane glycoprotein on the surface of epithelial cells [56]. In a phase IIb study, L-BLP25 demonstrated a survival benefit over best supportive care alone in patients with stage IIIB or IV non-small cell lung cancer (17.2 months vs. 13 months; HR 0.745; 95% CI 0.533–1.042) with the most pronounced effect seen in stage IIIB locoregional disease (HR 0.548; 95% CI 0.301–0.999) [57]. According to tumour biology (estimated by receptor status, grading, and Ki67), patients will receive neoadjuvant chemotherapy or endocrine therapy and will be randomized to additional immunotherapy with L-BLP 25 or control. For the first time in neoadjuvant ABCSG trials, the RCB score is defined as primary study endpoint. A second randomization will be performed within the chemotherapy cohort: Patients will receive the conventional historical sequence of anthracyclines followed by docetaxel, or a reversed sequence starting with docetaxel. Indeed, 3 phase II trials suggested that a higher chemotherapy dose intensity is achieved when taxanes are administered first [58–60], which is an important aspect in light of the Norton-Simon hypothesis [61]. In the neoadjuvant setting, a single large randomized study observed a pCR rate of 20% with a reverse sequence design compared to 15% with the conventional sequence [62]. Furthermore, a retrospective analysis of 3,010 patients treated at the MD Anderson Cancer Center even reported a lower risk of relapse and death when paclitaxel was administered first [63].

Conclusion

Neoadjuvant chemotherapy today is a well established option in the treatment of patients with early stage breast cancer. Most modern regimens encompass anthracyclines and taxanes, often applied in a sequential design, with highest pCR rates observed in triple-negative disease; incorporation of further drugs such as capecitabine might further improve outcome in selected patients, although data are not unanimous. Platinum salts may be an effective alternative in patients harbouring BRCA-1 mutations, but data from phase III trials are still missing. Trastuzumab has evolved as mainstay for the preoperative treatment of Her2-positive patients, with pCR rates of approximately 50%. Other targeted drugs such as lapatinib or pertuzumab have already shown promising results within clinical trials. Due to conflicting data, the exact role of bevacizumab awaits further clarification.

Disclosure Statement

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