Neoadjuvant treatment for HER-2-positive and triple-negative breast cancers

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Neoadjuvant therapy (NT) has become a valuable research tool for the incorporation of alternative cytotoxic agents, as well as new biological therapies, into anthracycline and taxane chemotherapy-based regimens. Her-2-positive disease is predictive of higher pathological complete response (pCR) to neoadjuvant chemotherapy and trastuzumab. Benefits were also seen for the combination of trastuzumab with lapatinib or pertuzumab, suggesting that dual blockage of the HER-2 will probably emerge as the new standard. Triple-negative phenotype is also predictive of high pCR to NT, but the prognosis of patients whose tumours do not achieve a pCR after neoadjuvant chemotherapy with anthracyclines and taxanes is dismal. Currently, it is recommended to use the same chemotherapy regimens as in non-triple-negative disease. The suggested benefit of neoadjuvant platinum, mainly in BRCA1-related cancers, needs to be confirmed in large randomized trials. Bevacizumab combined with neoadjuvant chemotherapy yields increased pCR compared with non-bevacizumab treatment, in large randomized data recently published. One study suggested higher benefit in triple-negative tumours. Long-term follow-up of these trials is needed to understand the role of bevacizumab treatment in BC and its important to find predictive biomarkers of response to this drug.

Key words: breast cancer, HER-2, neoadjuvant systemic therapy, triple negative

general considerations

the aims of neoadjuvant therapy in breast cancer

Neoadjuvant therapy (NT), also called primary systemic treatment, is the standard of care for women with locally advanced, inflammatory or inoperable primary breast cancer (BC) [1–4]. The demonstration by the landmark NSABP B-18 trial [5, 6] that NT offered the same survival benefits as postoperative treatment has moved NT to the context of operable disease, looking for the surgical advantages of tumour downstaging. Subsequently, the NSABP B-27 [7] trial and other studies [8–10] have shown that patients with pathological complete response (pCR) to NT have improved disease-free (DFS) and overall survival (OS), suggesting its use as a surrogate marker for trials comparing different schedules of primary systemic therapy. Currently, NT is generally used to improve the surgical options, to determine the response to chemotherapy and to obtain long-term DFS. Additionally, NT is an important research tool for evaluating the effect of new therapies on BC biology and outcome. It allows a rapid integration of new molecular diagnostic and prognostic techniques, stratification for molecular heterogeneity and incorporation of new biological therapies into the design of clinical trials.

is there an optimal chemotherapy regimen for the neoadjuvant setting?

Anthracycline/taxane-based chemotherapy regimens have been the most extensively studied, but so far no specific regimen has been found to be clearly superior. Incorporation of taxanes has increased the response rates [11–13], with large phase III trials reporting pCR rates of 15%–20% [14]. These, however, have not always translated into better long-term outcomes, namely better DFS or OS. Regimens tested include AC followed by docetaxel; combination of docetaxel, doxorubicin, cyclophosphamide; combination of epirubicin, paclitaxel, cyclophosphamide, methotrexate, fluorouracil; addition of capectabine to a sequence AC and docetaxel; and a dose-dense sequence of epirubicin and paclitaxel. Administration strategies have included the sequential, concurrent and both sequential and concurrent delivery of agents as well as dose-dense approaches [14–16].

Tailoring treatment to response has also been tested in several studies, as the GeparTrio trial from the German Breast Group [15, 17], The Aberdeen [13] and MD Anderson trials [18], but so far it is not yet clear which group of patients benefit the most from changing to a non-cross-resistant regimen.

predictors of response to neoadjuvant treatment

There has been an effort to establish biological markers predictive of pCR to NT. A large retrospective analysis from the MD Anderson Cancer Center (MDACC) group [19] identified estrogen receptor (ER)-negative disease predictive of...
higher rate of pCR, regardless of the drug regimen or duration of chemotherapy (90% of patients received anthracycline-based chemotherapy, and 66% received additional taxane therapy). Evidence is also available from prospective studies. The integrated meta-analysis [20] on individual data from the German Breast Group and the AGO Breast Group provides information on 6402 patients enrolled in neoadjuvant trials containing doxorubicin or epirubicin, docetaxel or paclitaxel, with or without trastuzumab. This has shown that ER-negative patients had a greater chance of pCR than ER-positive patients [OR 3.2 (95% CI: 2.7–3.8); P < 0.0001]. Furthermore, HER-2-positive disease [OR 2.2 (95% CI: 1.8–2.5); P < 0.0001], higher grade [OR 1.8 (95% CI: 1.5–2.2); P < 0.0001], younger age [OR 1.3 (95% CI: 1.2–1.6); P = 0.0001], non-lobular-type tumours [OR 1.7 (95% CI: 1.2–2.3); P = 0.001] and smaller tumour size [OR 1.5 (95% CI: 1.2–1.9); P = 0.0006] were also significant predictors of pCR.

Despite the fact that tumours lacking expression of ER have higher pCR, exceeding 40% in some studies, patients survival with this phenotype is still shorter than patients with hormonal receptor-positive disease [21]. For lobular tumours, the majority of which are ER-positive, and luminal A BC, the lower response rates seen with neoadjuvant chemotherapy do translate into a worse OS [20, 22, 23]. This is related to the fact that both these types of BC usually do not respond well to chemotherapy but have high endocrine responsiveness.

HER-2 overexpression/amplification predicts response to treatment with the monoclonal antibody trastuzumab [24], and has also been associated with better response to anthracyclines [25, 26]. Whether the latter effect is linked to the co-amplification of topoisomerase IIα is still a matter of debate, and mixed results have been obtained [26, 27]. An association between HER-2 positivity and response to taxanes has also been suggested [28] but warrants further investigation.

Mutations in p53 were postulated to be predictors of pCR in some studies, particularly predictive for a response to taxanes [29, 30], while in other studies no clinical prediction or a negative one was found [31, 32]. To validate the hypothesis of a predictive value of p53 mutations for a response to taxanes, a large randomized multicentric neoadjuvant trial (EORTC 10994/BIG 1–00) was carried out; its results do not support this hypothesis [33].

Triple-negative breast cancer (TNBC) has also been shown to be associated with higher response rates to NT compared with non-triple-negative tumours in several studies such as the German neoadjuvant meta-analysis [20], the I-SPY 1 study [23] and the large retrospective analysis of the MDACC [34]. In this last one, 1118 patients with stage I–III disease were included, and pCR rates were 22% in TNBC patients versus 11% in non-TN (P = 0.034). Still, TNBC patients had worse survival (3-year DFS and OS). The important finding was that if pCR was achieved, patients with TNBC and non-TNBC had similar survival (P = 0.24), while if residual disease was found the TNBC group had significantly worse OS (P = 0.0001).

Higher pCR rates have been also reported to be associated with high Ki-67 expression, a marker of proliferation [35], and decreases in Ki-67 expression were found to correlate with increased apoptosis in MCF-7 human BC xenografts when deprived of estrogen [36].

Continuous proliferation leading to continuous genomic instability might be responsible for a high rate of pCR, regardless of the drug regimen or duration of chemotherapy (90% of patients received anthracycline-based chemotherapy, and 66% received additional taxane therapy).

Gene expression profiling has suggested a new molecular classification of BC and has contributed for a better understanding of BC heterogeneity, aiming a better treatment tailoring [37–39]. The ER-positive and ER-negative BC were further divided into subgroups with different phenotypes and diverse prognostic outcomes.

Some studies have generated preliminary gene signatures with potential predictive value for docetaxel and paclitaxel plus fluorouracil, doxorubicin, cyclophosphamide [40, 41]. However, these signatures have not yet been validated in subsequent studies and no such tool exists for use in clinical practice.

More recent studies suggest that prediction of response to a specific chemotherapy agent is different among the different BC subtypes and is more likely to be achieved by using multifactorial tools [34, 42–45].

**neoadjuvant systemic therapy for HER-2-positive BC**

The recent international panel on NT recommended that trastuzumab, the humanized monoclonal antibody targeting HER-2, should be incorporated into the NT chemotherapy regimen in patients with HER-2-positive disease [46]. The first reported randomized trial from the MDACC showed a very high pCR rate of 65.2% in patients treated with trastuzumab (versus 26%) [47, 48]; these results led to a premature closure of the study but, unfortunately, such high pCR rates have not been reproduced in other studies. In this study, no safety concerns were raised related to concurrent treatment with anthracycline, with no cases of cardiac clinical dysfunction or cardiac deaths.

Additional data on neoadjuvant trastuzumab come from the NOAH trial [49], where 228 HER-2-positive BC patients were randomly assigned to receive a neoadjuvant chemotherapy regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate and fluorouracil with or without trastuzumab given concurrently. Patients further received adjuvant trastuzumab for a total of 1 year. A parallel cohort of 99 patients with HER-2-negative disease was included and treated with the same chemotherapy regimen. Trastuzumab-treated patients had a substantial improvement of event-free survival at 3 years, with a hazard ratio of 0.59 (95% CI: 0.38–0.90). Only two patients (2%) developed symptomatic cardiac failure that responded to treatment, and no cardiac deaths were reported. The German GeparQuattro study [16, 50] also evaluated neoadjuvant trastuzumab. This randomized phase 3 trial assessed the incorporation of capecitabine in an anthracycline/taxane-based regimen and the concurrent use of trastuzumab with these chemotherapy regimens in HER-2-overexpressing patients. Of 1509 patients included, 445 patients had HER-2-positive BC and received trastuzumab (6 mg/kg) every 3 weeks concomitant with all chemotherapy cycles. pCR rate was higher in HER-2-positive disease compared with the HER-2-negative group (31.7% versus 15.7%). In the subgroup of patients that did not respond to epirubicin/
cyclophosphamide, the pCR rate was also higher in HER-2-positive versus HER-2-negative tumours (16.7% versus 3.3%). Grade 3 and 4 neutropenia as well as conjunctivitis were seen in the trastuzumab-treated group, but there were no cardiac safety concerns.

Lapatinib is an oral dual-tyrosine kinase inhibitor that targets EGFR and HER-2, and has been tested in the NT setting, both as a single agent and in combination with trastuzumab. In the NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) study [51], 455 patients were randomly assigned to receive oral lapatinib (1500 mg), i.v. trastuzumab (loading dose of 4 mg/kg, subsequent doses of 2 mg/kg) or lapatinib (1000 mg) plus trastuzumab. Patients received anti-HER-2 therapy alone for 6 weeks initially and then combined to weekly paclitaxel (80 mg/m²) for 12 weeks before surgery. After surgery, patients received adjuvant chemotherapy followed by the same targeted therapy as in the neoadjuvant phase for 52 weeks. Combination of lapatinib and trastuzumab yielded a substantially higher pCR rate than the monotherapy arms. The response to lapatinib was numerically lower than to trastuzumab, although the difference did not reach statistical significance. The dual combination was associated with higher toxicity, mainly diarrhoea (grade 3 in 23.4% patients), and liver enzyme alterations consisted mainly in transient and reversible rise in transaminases (grade 3 in 17.5% patients and treatment discontinuation in 30 patients). This trial also confirmed the finding from previous studies of higher pCR rate in ER-negative tumours compared with ER-positive ones.

Lapatinib has also been compared with trastuzumab treatment in the Geparquinto trial [52], a phase 3 randomized trial that enrolled 620 untreated HER-2-positive patients with operable or locally advanced BC. Patients were randomly assigned to receive four cycles of epirubicin (90 mg/m²) plus cyclophosphamide (600 mg/m²) and four cycles of docetaxel (100 mg/m²), every 3 weeks, with either trastuzumab 3 weekly (6 mg/kg/loading dose of 8 mg/kg) or lapatinib (1000–1250 mg) throughout all cycles before surgery. Main results have shown a substantially higher pCR rate for the trastuzumab treatment arm (30.3%) compared with lapatinib (22.7%). Trastuzumab treatment was more associated with oedema (39.1% versus 28.7%) and dyspnoea (29.6% versus 21.4%), and lapatinib more with diarrhoea (75.0% versus 47.4%) and skin rash (54.9% versus 31.9).

Taken together, the results of these two studies have led to the recommendation that lapatinib should not be used as a single (neo)adjuvant anti-HER-2 target outside clinical trials. Additionally, patients treated with lapatinib monotherapy in the large adjuvant ALTTO trial were informed about these results and proposed to receive adjuvant trastuzumab, which, although necessary, will impact on the long-term results of this study. The reasons for these disappointing results of lapatinib in early BC are not yet fully understood. Several hypotheses have been speculated, such as lower capacity to block the HER-2 pathway compared with trastuzumab; a higher efficacy of trastuzumab due to the additional tumour effect by the antitumour antibody-derived cellular cytotoxicity process; or a lower drug exposure related to dose reductions and low adherence linked to its higher toxicity. Finally, an important finding of this study is related to the cardiac safety of the concurrent administration of trastuzumab and anthracyclines, with only one patient experiencing congestive heart failure.

In the similarly designed phase 2 randomized CHER-LOB study, patients were randomly assigned to receive weekly trastuzumab, lapatinib (1500 mg orally daily) or trastuzumab plus lapatinib (1000 mg, p.o.), concurrently with chemotherapy. The chemotherapy regimen used was weekly paclitaxel (80 mg/m²) for 12 weeks, followed by FEC (fluorouracil, epirubicin and cyclophosphamide) for four courses. Results were recently published [53], showing higher pCR for the combination of trastuzumab and lapatinib (46.7%). Diarrhoea, dermatologic toxic effects and hepatic toxic effects were observed more frequently in patients receiving lapatinib. No cases of congestive heart failure were noticed.

The new anti-HER-2 humanized monoclonal antibody pertuzumab acts through the inhibition of receptor dimerization, through the NeoSphere trial [54]. This was a phase II randomized trial designed to test the antitumour activity and tolerability of the combination of docetaxel, trastuzumab and pertuzumab (THP), compared with trastuzumab plus pertuzumab (HP), docetaxel and pertuzumab (TP) and docetaxel and trastuzumab. Cycles were given intravenously q3w: pertuzumab, 840 mg loading dose and 420 mg maintenance; trastuzumab, 8 mg/kg loading dose and 6 mg/kg maintenance; docetaxel, 75 mg/m² with escalation to 100 mg/m² if the starting dose was well tolerated. After surgery, all patients received trastuzumab to 1 year and three cycles of FEC; in case of neoadjuvant HP, they also received trastuzumab before FEC. The pCR was significantly higher (P = 0.014) for the combination of docetaxel with both anti-HER-2 target agents (THP), with good tolerability, namely cardiac safety.

These studies, together with important evidence from two trials in the metastatic setting [55, 56], provide strong evidence that the dual blockade of the HER-2 receptor has superior efficacy and may soon become standard of care. Nevertheless, many questions remain unanswered such as (i) which is the optimal combination of anti-HER-2 agents; (ii) which is the best chemotherapy regimen to use with these agents; (iii) can chemotherapy be avoided in some patients when a dual-blockade strategy is used; (iv) what is the role of dual HER-2 blockade in combination with endocrine therapy for HER-2-positive and ER-positive BC; (v) can we identify reliable biomarkers predictive of response to each specific anti-HER-2 agent or combination. Intensive research will undoubtedly continue for this specific BC subtype.

**neoadjuvant systemic therapy for triple-negative BC**

One of the most active areas of research in BC relates to tumors with triple negative phenotype or TNBC, which is characterized by lack of expression of both estrogen and progesterone and HER-2 receptors [57]. About 70% of TNBC belong to the basal-like molecular subtype. There are also rarer histological types of BC that have the triple-negative...
phenotype. At the present time, chemotherapy is the only proven therapy for this usually very aggressive BC subtype, and for the neoadjuvant and adjuvant settings all international guidelines recommend the use of the same regimens as for non-TNBC, i.e. an anthracycline/taxane-based regimen. Small studies have suggested that platinum may be particularly effective for TNBC, with pCR rates of 54.6% with four cycles of neoadjuvant docetaxel and carboplatin [38], 40% with erubicin, cisplatin and fluorouracil, followed by weekly paclitaxel [59], and 80% with cisplatin in a BRCA1 mutation patient population [60]. On the other hand, a pCR of 20% was reported with neoadjuvant cisplatin monotherapy [61]. These data are based on small studies and need further validation in larger randomized studies, specially for non-BRCA-related TNBC.

In a combined analysis of two International Breast Cancer Study Group (IBCSG) trials (VIII and IX) [62], classical CMF was shown to be quite effective for TNBC. Recent data from two large neoadjuvant prospective trials [63, 64] suggest improved response rates with the combination of bevacizumab with neoadjuvant chemotherapy. In the study run by the German group [63], patients with HER-2-negative BC received four cycles of neoadjuvant erubicin and cyclophosphamide and were then randomly assigned to receive docetaxel with or without concomitant bevacizumab. The pCR rate was higher in the bevacizumab group (OR 1.29 (95% CI: 1.02–1.65), P = 0.04), and, for the 633 patients with TNBC, this difference was of higher magnitude (39.3% versus 27.9%; OR = 1.67, P = 0.003). However, the P-value for the interaction test was not significant. Furthermore, the addition of bevacizumab was associated with higher toxicity, specific of bevacizumab such as bleeding and arterial hypertension, as well as febrile neutropenia, infections, mucositis and hand–foot syndrome. The NSABP-B40 study [64] has shown similar results, with higher pCR rates when chemotherapy was combined with bevacizumab (34.5% versus 28.2%, P = 0.02), but also at the expense of increased toxicity. In this study, patients were randomly assigned to receive docetaxel monotherapy, docetaxel plus capecitabine or docetaxel plus gemcitabine for four cycles, with all regimens followed by treatment with doxorubicin–cyclophosphamide for additional four cycles. Patients were also randomly assigned to receive or not bevacizumab during the first six cycles of treatment and after surgery for 10 doses. Contrary to the German study, the subgroup analysis revealed a more pronounced effect of bevacizumab in hormonal receptor-positive disease. The authors speculated the disparity of inclusion criteria, different chemotherapy regimen sequencing and bevacizumab combination as possible reasons for these results. Importantly, none of these trials have long-term follow-up, which is indispensable to understand whether the highest pCR rates will translate into better long-term outcomes such as better DFS or OS. Similar to the situation for metastatic BC, further research is needed to identify clear predictive biomarkers of response to bevacizumab that will help selecting the patients who may benefit from the addition of this toxic and expensive drug.

The dismal prognosis of TNBC patients whose tumours do not achieve a pCR after neoadjuvant chemotherapy with anthracyclines and taxanes [34] renders the development of efficacious new therapies for this BC subtype a major research priority.

disclosure

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references


