

Targeted and Osteo-Oncologic Treatment in Early Breast Cancer: What Is State-of-the-Art and What Might Become so within the Next 5 Years?

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Summary

In 2014, modern strategies of targeted therapies in the adjuvant setting are mainly focused on anti-human epidermal growth factor receptor 2 (HER2) blockade. For the 15% of HER2-enriched tumors, 1 year of treatment with the monoclonal antibody trastuzumab is the standard of care. All patients, regardless of tumor size, nodal status, or age, profit from therapy with risk reduction rates for recurrence of up to 50%. As a consequence, the current guidelines recommend the use of trastuzumab in these patients if additional risk factors lead to the consideration of adjuvant chemotherapy. The concurrent use with taxane-based chemotherapy is preferred. The concept of dual HER2 blockade – already approved in the metastatic setting – shows also significantly improved efficacy in neoadjuvant trials. Dual blockade with trastuzumab and pertuzumab is approved by the Food and Drug Administration (FDA) for neoadjuvant treatment of HER2-overexpressing tumors. However, until approved in Europe, this treatment approach remains off-label for early breast cancer and study participation is highly recommended. Bisphosphonates (BPs) and denosumab are approved in breast cancer as standard therapy for the treatment of bone metastases. In the adjuvant setting, BPs and denosumab can be given to prevent tumor therapy-induced bone loss. The antineoplastic effect of BPs in the adjuvant setting and its role in the prevention of metastatic disease are still under discussion.

Introduction

In breast cancer, the principle of targeted therapy is well established. Besides endocrine treatment as a therapeutic principle known for decades, modern strategies of targeting breast cancer focus on drugs interfering with molecular mechanisms that have a major impact on cell biological behavior such as proliferation, angiogenesis, and metastasis.

The characterization of human epidermal growth factor receptor 2 (HER2) represents the most important milestone in the development of innovative, targeted therapeutic concepts in breast cancer within the last decade. Its overexpression leads to strongly increased proliferation rates, with a more aggressive and unfavorable consecutive course of disease [1].

With the implementation of distinct molecular subtypes of breast cancer into clinical practice, a specific and targeted therapeutical approach is getting more feasible. The HER2-positive subtypes, as determined by immunohistochemistry (IHC), represent about 15% of all breast cancers and can be targeted with the humanized monoclonal antibody trastuzumab. In early breast cancer, the antibody is given if the patient is receiving adjuvant or neoadjuvant chemotherapy.

According to international and national guidelines, HER2 positivity as the obligatory prerequisite for a trastuzumab-based therapy is defined as:

- protein overexpression detected by IHC with a score of +3 (> 10% of intensive and complete staining) or
- HER2 gene amplification detected by in situ hybridization techniques such as fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) [2].

The evidence for adjuvant treatment with trastuzumab is based on 5 international multicenter randomized trials with over 13,000 patients and 2 meta-analyses. Overall, the addition of trastuzumab to chemotherapy led to a significant reduction of recurrence ($p < 0.00001$) and metastasis ($p < 0.0001$) and to improved survival ($p < 0.00001$). The risk

of recurrence was reduced by 50% with the trastuzumab treatment [3, 4].

The HERA trial included more than 5,090 nodal-negative and -positive patients. As a sequential therapy, patients received different regimens containing anthracyclines with or without taxanes and trastuzumab after completion of chemotherapy [5, 6]. Trastuzumab was administered for 1 or 2 years with a loading dosage of 8 mg/kg followed by 6 mg/kg every 3 weeks. The second interim analysis of the 1-year trastuzumab treatment arm revealed a significant reduction of recurrence by 46% ($p < 0.0001$), independent of the preceding chemotherapy regimen and lymph node or hormone receptor (HR) status. The risk of death was significantly reduced by 44% [6]. The final analysis with an 8-year follow-up, which also included the 2-year trastuzumab application, confirmed the recent significant findings without a benefit regarding the prolonged treatment [7].

The 2 US trials National Surgical Adjuvant Breast and Bowel Project (NSAPB) B-31 und North Central Cancer Treatment Group (NCCTG)-N9831 presented with a similar design and used paclitaxel either weekly or 3-weekly in combination or sequentially with trastuzumab (loading dose 4 mg/kg, maintenance dose 2 mg/kg weekly) after 4 cycles of doxorubicin and cyclophosphamide (AC). The concurrent treatment arms of both trials were evaluated as a joint analysis. The fully published study with 3,351 patients showed a significant reduction of recurrence (52%) and breast cancer-related mortality (33%) [8].

The Breast Cancer International Research Group trial 006 (BCIRG 006) investigated an anthracycline-free regimen of $6 \times$ docetaxel and carboplatin plus trastuzumab (TCH) with similar efficacy as AC followed by docetaxel and trastuzumab (AC-TH) [9]. The concurrent application of trastuzumab led to a significant reduction of recurrence (TCH vs. AC-TH, hazard ratio (HR) 0.64; $p = 0.06$) [10].

In this context, the potential cardiotoxicity of trastuzumab in patients receiving trastuzumab in addition to chemotherapy has to be considered. The NSABP B-31 5-year update identified 4 risk factors for heart failure in trastuzumab-treated patients: age (50–59 years, 5.1%; > 60 years, 5.4%), use of hypertensive medications (6.8%), baseline left ventricular ejection fraction (LVEF) values of 50–54% (12.9%), and post-anthracycline chemotherapy LVEF values of 50–54% (12.6%). The anthracycline-free regimen in the BCIRG 006 trial was characterized by a significantly lower rate of symptomatic heart failures grades 3/4 and LVEF declines of > 10% compared to the anthracycline-containing arm. With an incidence rate for congestive heart failure of 0.4%, which is in the same range as for the anthracycline-containing, trastuzumab-free treatment arm (0.7%), the TCH regimen is a valuable option in patients at risk as defined above [10].

Overall, consequent cardiac monitoring by echocardiography (LVEF) or multigated acquisition (MUGA) scan is recommended and should be performed 3-monthly during

trastuzumab treatment. In case of LVEF alterations, individualized therapy guidance with intensified monitoring up to a complete stop of trastuzumab application might be indicated [2].

Duration of Treatment

The optimal duration of treatment with trastuzumab is considered to be 1 year. Since the final analysis of the HERA trial did not show any advantage for the 2- versus the 1-year treatment regimen, the efficacy of shortened trastuzumab application remained unclear. The FinHer trial demonstrated a significant benefit for a small cohort of patients ($n = 232$) with a 9-week trastuzumab regimen [11]. However, the data of the French PHARE trial ($n = 3,000$) stand in clear contrast to these findings. The 6-month versus the 12-month standard treatment failed to prove non-inferiority with regard to disease-free survival (DFS) (13% vs. 10.4%; HR = 1.28) and overall survival (OS) (HR = 1.47) [12].

Treatment Schedules

Both sequential and concurrent use of trastuzumab are possible options. The actual recommendations, which favor the concurrent use of trastuzumab with taxanes, are mainly based on a subgroup analysis of the NCCTG-N9831 trial. A significant benefit for the concurrent versus sequential use of trastuzumab was found, even though the p value was not significant after correction for multiple testing as stated in the study protocol [13]. In concordance with these findings, the recent meta-analysis by Yin et al. [4] supported this benefit. However, the routine use of concurrent trastuzumab and anthracyclines in patients without cardiac risk factors should be carefully considered, even if data on tolerable cardiac toxicity exist.

As an additional aspect of adjuvant treatment combinations, the existing data also support the administration of trastuzumab concurrent to adjuvant radiotherapy of the breast or thoracic wall [14].

Patient Selection

In all trials the benefit of trastuzumab treatment in HER2-positive patients was evident independent of tumor size, age, and nodal status. In HERA and BCIRG 006, patients with tumor sizes of less than 1 cm were also included [10]. The estimated 5-year rates of DFS for these subgroups were 86% in the AC-TH group and 86% in the group receiving TCH, as compared with 72% in the AC-T group (AC followed by docetaxel). Together with the existing knowledge of HER2 as a strong prognostic factor for patients with small, node-

negative, HER2-positive tumors < 1 cm, for local as well as distant recurrence [15], these findings led to the current guidelines recommendations to administer trastuzumab in patients with tumors of 0.5–1.0 cm, if additional risk factors lead to the consideration of adjuvant chemotherapy [2].

Neoadjuvant Chemotherapy

There is also a large body of evidence for the use of trastuzumab in combination with chemotherapy for patients with HER2-positive breast cancer in the neoadjuvant setting [16–21]. As in the adjuvant approach, these randomized trials demonstrated also a significant benefit for trastuzumab. Compared to chemotherapy alone, neoadjuvant trastuzumab plus chemotherapy significantly increased the pathologic complete response (pCR) rates [16–19]. For the specific subgroup of patients with HER2-positive tumors, pCR is a strong surrogate for improved outcome and is associated with improved DFS, distant DFS, and OS [17, 20–23].

Future Perspectives of Targeted Treatment

For the HER2-directed treatment, a subcutaneous formulation using hyaluronidase has been developed. In the international phase III (neo)adjuvant HannaH trial, 596 patients with HER2-positive breast cancer were randomized to 8 cycles of neoadjuvant chemotherapy (4 × docetaxel, followed by 4 × epirubicin/cyclophosphamide) concurrently given to trastuzumab every 3 weeks either intravenously (i.v.) (loading dose 8 mg/kg, maintenance dose 6 mg/kg) or subcutaneously (s.c.) (fixed dose 600 mg). After surgery, patients continued their trastuzumab treatment to complete 1 year of trastuzumab treatment [24].

Primary endpoints comprised pharmacokinetic profiles with trastuzumab serum levels, pCR rates, and safety. Interestingly, the HannaH trial showed no difference in the serum levels for the fixed dose of s.c. applied trastuzumab versus the weight-adapted i.v. applied antibody. Furthermore, the safety features were also comparable between groups with similar grade 3–5 adverse events; however, more patients presented with serious adverse events in the s.c. group, which was mainly attributable to infections and infestations (8.1% vs. 4.4%) in this group. The pCR rates demonstrated an equi-effective activity for s.c. (45.4%) versus i.v. administered trastuzumab (40.7%) [24]. The PrefHer trial assessed the patients' preference for either s.c. or i.v. trastuzumab in 248 patients. The s.c. application was preferred by 91.5% of the intention-to-treat (ITT) population [25]. Overall, the pharmacokinetic profile together with the proven high efficacy of s.c. trastuzumab and the simplified and abridged application modus (approximately 5-min s.c. application) offer an innovative and interesting alternative option in the treatment of HER2-positive

breast cancer and led to the approval of the drug formulation in 2013.

The neoadjuvant chemotherapy setting opens the field for innovative drugs and treatment regimens. Over the last years, the concept of dual inhibition of HER2 gained a broad basis of evidence. This was shown for the combination of chemotherapy plus anti-HER2 treatment with trastuzumab plus lapatinib or pertuzumab [26–28]. The optimized efficacy of these treatment regimens with increased pCR rates led to the approval of pertuzumab in the neoadjuvant setting in the USA, but so far not in Germany. There is also evidence for good efficacy of chemotherapy-free regimens combining 2 anti-HER2 agents, which might be feasible for certain subgroups of patients, which still have to be identified [26, 29].

Overall, the dual inhibition concept for early HER2-positive breast cancer will become standard of care in the near future. However, until approval, these treatment concepts cannot be valued as standard of care and should only be applied in the setting of clinical studies.

Treatment of triple-negative breast cancer (TNBC) is one of the most important challenges in the current research field. Since the classical treatment targets are missing, innovative strategies are desperately needed. A potential targeted treatment option might be bevacizumab. The phase III GeparQuinto trial reported a significantly higher pCR rate for the combination of chemotherapy and bevacizumab in comparison to chemotherapy alone in this patient subgroup [30]. The NSABP B-40 trial, however, found this effect of bevacizumab predominantly in luminal HR-positive breast cancers [31]. Furthermore, the BEATRICE phase III trial investigated the antibody as an additional treatment to chemotherapy in unselected patients with TNBC, but did not show any benefit in this patient cohort [32]. In the Cancer and Leukemia Group B (CALGB)/Alliance 40603 study, the addition of bevacizumab to standard neoadjuvant chemotherapy for TNBC was investigated. For bevacizumab, a significantly improved pCR rate was observed for the breast (59% vs. 48%, $p = 0.00089$) but not for the breast plus axilla (52% vs. 44%, $p = 0.057$), in comparison to patients not receiving the antibody. However, 23% of the patients had to discontinue treatment with bevacizumab. Major side effects were more common in this treatment group [33]. These controversial results need further exploration, and bevacizumab can momentarily not be considered as a standard-of-care treatment for TNBC.

Bone-Targeted Therapy in Early Breast Cancer

Bisphosphonates (BPs) and denosumab are approved in breast cancer as standard therapy for the treatment of bone metastases. They reduce the prevalence of skeletal-related events (SRE) including fractures and hypercalcemia. In the adjuvant setting, BPs and denosumab can be given to prevent and treat tumor therapy-induced bone loss in pre- and post-

Table 1. Summary of clinical trials investigating bisphosphonates (BPs) in the adjuvant setting

Authors/Study	Type of BP	Mode	Schedule	Dose, mg	Duration, years	Benefit, premenopausal	Benefit, postmenopausal
Saarto et al. [41]	clodronate	p.o.	daily	1,600	3	no	no
Diel et al. [39]	clodronate	p.o.	daily	1,600	2	OS, bone metastasis-free survival	
Powles et al. [40]	clodronate	p.o.	daily	1,600	2	bone relapse-free survival	
NSABP-B34 [42]	clodronate	p.o.	daily	1,600	3	no	only for recurrence-free interval (> 50 years)
GAIN [50]	ibandronate	p.o.	daily	50	2	no	no
ZO-FAST [46]	zoledronate	i.v.	every 6 months	4	5	not included	DFS
ABCSG-12 [44]	zoledronate	i.v.	every 6 months	4	3	DFS, OS	not included
AZURE [47]	zoledronate	i.v.	different doses ^a	4	5	no	DFS, OS (> 60 years or 5 years postmenopausal)
NATAN [49]	zoledronate	i.v.	different doses ^a	4	5	no	no

^aq3–4 weeks for the first 6 doses, q3 months for 8 doses, followed by q6 months to complete 5 years.

menopausal women, even if there is so far no approval for this specific indication [34–37]. The antineoplastic effect of BPs including zoledronate and clodronate has been demonstrated in the adjuvant setting by several studies. However, due to conflicting results, their role in the prevention of metastatic disease is still under discussion. For denosumab, clinical trials have been initiated, but results are pending. Therefore, only the role of BPs including zoledronate, clodronate, and ibandronate in the adjuvant setting will be elucidated.

Clodronate

The first data on the adjuvant effects of the BP clodronate were provided by Diel et al. [38]. In a prospective clinical trial, 302 breast cancer patients were randomly assigned to receive oral clodronate (1600 mg/day) for 2 years or standard follow-up. An updated survival analysis with a median follow-up of 103 months showed that patients treated with clodronate showed a significant improvement in OS ($p = 0.049$) compared to those without [39] (table 1). Powles et al. [40] demonstrated a significant improvement in the 5-year bone relapse-free survival by adding oral clodronate for 2 years, in their trial involving 1,089 adjuvant breast cancer patients. In contrast, the study by Saarto et al. [41] could not demonstrate such an effect for clodronate. Conflicting results were also reported from the randomized, double-blind, placebo-controlled NSABP B-32 trial involving 3,323 patients with primary breast cancer. Patients were randomly assigned to either oral clodronate 1600 mg daily for 3 years ($n = 1,662$) or placebo ($n = 1,661$). After a follow-up of 8.4 years, no benefit could be observed for DFS and OS. However, in the subgroup of patients aged 50 years and older, a significant improvement in recurrence-free interval but not for OS was obtained [42].

Zoledronate

More evidence for the antineoplastic effect of BPs was accumulated when the results from studies evaluating zoledronate as a bone-protective agent in patients with endocrine treatment were presented.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 study compared endocrine therapy (goserelin

plus anastrozol vs. tamoxifen) alone with endocrine therapy plus zoledronate (4 mg i.v. every 6 months for 3 years). Data of 1,803 premenopausal women suffering from stage I–II HR-positive breast cancer demonstrated that adding zoledronate to endocrine therapy reduces the relative risk of disease progression by 32% at a median follow-up of 62 months [43]. The long-term follow-up at 82 months was recently presented [44]. Patients receiving zoledronate had a significant (27%) reduction in the risk of DFS events and a significant (41%) reduction in the risk of death versus no zoledronate. However, subgroup analysis revealed that benefit for DFS and OS was driven by patients older than 40 years.

For postmenopausal patients the Z-FAST and ZO-FAST trials investigated the efficacy of immediate versus delayed zoledronate (4 mg i.v. every 6 months for 5 years) to prevent therapy-related bone loss in patients with HR-positive stage I–III breast cancer receiving endocrine therapy (letrozole) [45]. As a secondary endpoint, a 34% relative risk reduction for DFS was demonstrated at 60 months for the ZO-FAST trial [46].

In contrast to the ABCSG-12 and Z-FAST/ZOFAST trials, the AZURE study was primarily designed to evaluate the antitumor activity of zoledronate combined with (neo)adjuvant chemotherapy in 3,360 pre- and postmenopausal patients with stage II/III breast cancer as a primary endpoint [47]. Patients were randomly assigned to receive standard adjuvant systemic therapy either with or without zoledronate (table 1). Zoledronate was not associated with a significant improvement in DFS or OS in the overall population after a median follow-up of 59 months. However, postmenopausal women (more than 5 years postmenopausal or > 60 years) with zoledronate showed improved OS and DFS rates. In a small subset of patients ($n = 195$) undergoing primary systemic treatment, the effect of zoledronate could be studied on the primary tumor. By adding zoledronate, the size of the primary tumor was significantly reduced by 43% compared with chemotherapy alone [48].

The role of zoledronate in a post-neoadjuvant setting was studied by the NATAN trial. Patients who did not reach complete response were eligible for this trial and were randomly

assigned to zoledronate versus observation. No benefit on clinical outcome could be observed by adding zoledronate. However, there was a trend toward longer DFS among postmenopausal patients 55 years of age or older receiving zoledronate [49].

Ibandronate

The GAIN study evaluated the efficacy of ibandronate in high-risk patients with more than 3 affected lymph nodes. 3,032 patients were randomly assigned to treatment with 2 different chemotherapy regimens and to ibandronate 50 mg orally or placebo for 2 years. This study was not able to show any benefit for DFS and OS. However, a trend toward longer DFS could be seen in patients older than 60 years treated with ibandronate [50] (table 1).

Recommendations for BPs in the Adjuvant Setting

Based on these results, only zoledronate (4 mg every 6 months) and oral clodronate (1600 mg per day) are currently recommended in postmenopausal women by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Mamma group [2]. The biological rationale for the benefit of BPs only for postmenopausal patients lies in the estrogen-deficient bone marrow microenvironment, which may lead to bone loss by increased osteoclast activity.

This AGO recommendation is supported by a current meta-analysis presented by Coleman et al. [51] at the San Antonio Breast Cancer Symposium (SABCS) 2013. The meta-analysis involved 36 trials with 17,791 patients. Among

all women, no significant differences were observed in the 10-year rate of all breast cancer recurrences. No effects were also seen on contralateral breast cancer incidence and local recurrence rate. However, among the subgroup of postmenopausal breast cancer patients, the distant recurrence rate was decreased by 3.5% and the bone recurrence rate by 2.9%. The rate of breast cancer mortality was 15.2% for those treated with BP versus 18.3% for those without BP. The risk reduction was seen irrespective of estrogen receptor (ER) and nodal status and use or non-use of chemotherapy. The benefits were similar for aminobiphosphonates and clodronate.

The length/scheduling of BP administration is not yet established, since the length of application varied from 2 to 5 years in the different clinical trials, as demonstrated in table 1. For premenopausal women, BPs should be considered for the prevention and treatment of therapy-induced bone loss.

In the adjuvant setting, denosumab can be given to prevent and treat tumor therapy-induced bone loss in pre- and postmenopausal women. The antineoplastic effect of denosumab is currently under investigation, e.g. in the D-Care study (NCT01077154). However, results will not be available within the next 1–2 years. Therefore, currently only clodronate and zoledronate can be offered to postmenopausal patients to improve disease outcome.

Disclosure Statement

E.S. and T.F. have nothing to disclose.

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