Adjuvant and Neoadjuvant Therapy with Lapatinib in ErbB2-Overexpressing Breast Cancer

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Introduction

Since 2001, when Sorlie et al. [1] introduced a molecular classification of breast cancer into at least 4 subgroups, the very heterogeneous prognosis of the different subtypes of this disease has been recognized. For clinical use, a more simple subclassification based on hormone receptor status and ErbB2 (HER2) status has been adopted, segregating hormone receptor-positive breast cancer with a relatively benign prognosis, and ErbB2-overexpressing breast tumor and triple-negative tumors with an unfavorable clinical outcome. Women with ErbB2-overexpressing tumors comprise up to 30% of all breast cancer patients and are characterized by a short relapse-free and overall survival [2]. The emergence of ErbB2 as a potential target for therapy and the combination of the anti-ErbB2 antibody trastuzumab with conventional cytotoxic regimens has led to a new era of breast cancer treatment [3].

Optimal Adjuvant Chemotherapy for ErbB2-Overexpressing Breast Cancer

An area of intensive investigation is the identification of subsets of breast cancer patients who benefit from specific chemotherapeutic regimens. In their pooled analysis from 7 randomized trials, Gennari et al. [4] reported a 29% reduction in the risk of relapse and a 27% reduction in mortality for trastuzumab-naïve patients with ErbB2-overexpressing breast tumors treated with anthracycline-based regimens compared to the ErbB2-negative cohort. The authors concluded that the superiority of these regimens seemed to be limited to ErbB2-overexpressing breast cancer. The increased responsiveness of tumors with a positive ErbB2 status to anthracyclines was thought to be at least partially explained by coamplification of ErbB2 and topoisomerase II alpha (TOP 2A), the enzyme for

DNA replication and recombination inhibited by anthracyclines. In a recent analysis of the Canadian trial NCIC CTG MA5, which compared 6 cycles CMF (cyclophosphamide/methotrexate/5-fluorouracil) versus CE₁₂₀F (cyclophosphamide/epirubicin/5-fluorouracil) in 710 premenopausal women, TOP 2A status, however, did not reach significance as a prognostic factor for disease-free or overall survival [5]. The TOP 2A status can, therefore, be characterized as an interesting area of research, but should not be assessed routinely in clinical practice. The predictive value of ErbB2 overexpression for a high responsiveness to taxanes is still a matter of debate.

The improved clinical efficacy seen with combinations of trastuzumab plus chemotherapy in the metastatic setting led to the initiation of 4 large adjuvant trials with this monoclonal antibody with a combined recruitment of more than 13,000 women with ErbB2-overexpressing early breast cancer. With the exception of trial BCIRG 006, these trials did not combine different cytotoxic schedules with trastuzumab. At present, it is therefore not possible to discriminate chemotherapeutic regimens optimally suited for the incorporation of trastuzumab. On the basis of the BCIRG 006 data, however, it can be concluded that trastuzumab can be effectively combined with a schedule of doxorubicin/cyclophosphamide (AC), followed by docetaxel and with carboplatin/docetaxel, with the latter having the advantage of less cardiotoxicity [6].

Unanswered Questions in Adjuvant Trastuzumab Therapy

Four adjuvant trials have demonstrated the benefit of adding trastuzumab to conventional chemotherapy in terms of improving recurrence-free and overall survival [6–8]. The positive results of the first interim analyses were confirmed by updates of NCCTG N9831 and NSABP B-31 as well as

BCIRG 006 [9, 10]. Based on these data guidelines recommending adjuvant treatment with trastuzumab for 1 year simultaneously with or up to 3 months after adjuvant chemotherapy were published [11]. Nevertheless, the optimal duration of trastuzumab treatment is still unclear. The aforementioned studies have reported results with 1 year of trastuzumab therapy. Results from the third arm of the HERA trial, testing 2 years of trastuzumab, are not yet available and are expected in 2008. The small FinHer trial showed an impressive relative risk reduction of 58% in disease-free survival with only 9 weeks of trastuzumab [12]. The short duration of trastuzumab therapy might be an advantage in terms of less cardiotoxicity, as no cases of congestive heart failure were documented in the FinHer trial. The applicability of these results to clinical practice is, however, limited by the small number of patients (n = 232) and few events (n = 12).

Delayed Adjuvant Treatment with Lapatinib: TEACH Trial

At present, there is a therapeutic gap for many patients with a diagnosis of early ErbB2-overexpressing breast cancer, who completed their primary therapy some years ago. At that time, these women did not receive adjuvant treatment with trastuzumab, because the results of the adjuvant trials cited above were not yet available. Moreover, there are no data to support the use of trastuzumab for these patients despite the high recurrence rate in this high-risk group.

Lapatinib is an oral receptor tyrosine kinase inhibitor (TKI) of both ErbB1 and ErbB2 and represents an alternative anti-ErbB2 treatment approach. On the basis of its promising activity and good tolerability in locally advanced and metastatic breast cancer, this small molecule is now moving into early breast cancer trials. The randomized, double-blind, multicenter, placebo-controlled TEACH (Tykerb Evaluation After Chemotherapy) study is the first to analyze the efficacy of lapatinib as delayed adjuvant therapy [13]. The aim of this phase III trial is to determine whether lapatinib, given for 1 year, will improve disease-free survival in women with early ErbB2-overexpressing breast carcinoma. Eligible patients must have an initial diagnosis of confirmed breast cancer (stage I–III), completed adjuvant chemotherapy, and no clinical or radiographic evidence of disease at study entry, and will be randomized to lapatinib (1,500 mg daily) or placebo. This trial is currently recruiting but is expected to reach its recruitment goal of 3,000 patients shortly.

Adjuvant Therapy with Lapatinib: ALTTO Trial

The current standard in the adjuvant anti-ErbB2 therapy, trastuzumab, is challenged in the 4-arm ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial, a joint effort of several international study groups. The ratio-

nale for the ALTTO trial is i) the potential development of resistance during or after adjuvant trastuzumab therapy; ii) the inability of the monoclonal antibody to cross the blood-brain barrier under physiological circumstances; and iii) concerns about the cardiac safety of trastuzumab.

In contrast to trastuzumab which prevents binding of growth factors at the extracellular ErbB2 domain, lapatinib works by inhibiting the intracellular tyrosine kinases of ErbB2 and ErbB1. Lapatinib has also demonstrated activity in tumor xenografts of p95-positive BT474 breast cancer cells that are characterized by a truncated version of ErbB2 and to which trastuzumab cannot bind [14]. Furthermore, lapatinib has shown high efficacy in trastuzumab-pretreated and resistant patients [15, 16], and has shown promising results in patients with central nervous system (CNS) disease [17]. In preclinical models, the addition of lapatinib to trastuzumab showed synergistic inhibitory effects on ErbB2-positive breast cancer cells [18]. Thus, it is conceivable that the combined treatment arm of lapatinib and trastuzumab in the ALTTO trial might offer an improved adjuvant strategy, with increased efficacy compared to each drug individually [18]. Lastly, because of the good tolerability of lapatinib and the low incidence of left ventricular ejection fraction (LVEF) decrease, this drug could provide a better risk-benefit ratio in the adjuvant setting.

In the ALTTO trial, patients with centrally determined early-stage ErbB2-overexpressing breast cancer (immunohistochemistry (IHC)3+ or fluorescent in situ hybridization (FISH)+) are randomized to single-agent trastuzumab or lapatinib or the combination of both drugs for 1 year. In a fourth study arm, patients are treated with trastuzumab for 3 months, followed by lapatinib for 7.5 months after a 6-week wash-out period (fig. 1). Eligible patients may have nodal-negative or positive disease and must present with an LVEF of at least 50%. The primary study endpoint is disease-free survival. Secondary endpoints are overall survival, time to recurrence, time to distant metastasis, safety and tolerability, and the cumulative incidence of brain metastases as first site of recurrence.

In 'Design I' of ALTTO, which is analogous to the design of the HERA trial, patients will have completed a minimum of 4 cycles of an anthracycline-based chemotherapy with or without a taxane before randomization. In 'Design II', the concomitant application of paclitaxel with the targeted therapy is allowed after completion of the anthracycline-based therapy. The great variability of possible chemotherapeutic regimens reflects the fact that ALTTO, as a globally recruiting study, has to account for different treatment patterns in the participating countries. Accepted 'feeder studies' for the ALTTO trial in Germany are: SUCCESS B, GAIN, and NNBC 3-Europe. Participants of these 3 trials can be randomized to one of the ALTTO arms after completion of chemotherapy.

A concomitant translational research program addresses critical issues, such as the clinical application of plasma proteomics or differential gene expression and the relevance of circulating tumor cells for the prediction of the risk of recurrence. This

Fig. 1. Design of the BIG 2.06/NCCTG N063D (ALTTO) Global Phase III ErB2 (HER2)+ Adjuvant Trial. Design 1: Completion of all (neo) adjuvant chemotherapy prior to targeted therapy. Patients with ER- or PgR-positive tumors receive endocrine therapy selected according to menopausal status; endocrine therapy will be started after the end of chemotherapy, will be administered concurrently with targeted therapies and will be planned for at least 5 years. Radiotherapy will be given if indicated.

Fig. 2. GEPARQUINTO trial: study treatment in the ErbB2-positive cohort. Postoperative treatment: hormonal therapy and/or bisphosphonates (Natan-Study).

translational research will be performed at 40 selected centers in Europe and 17 centers in the US. In total, the ALTTO trial will recruit 8,000 patients, 2,000 of which will be part of the translational research project. Until the end of February 2008, about 500 patients have been included in this large adjuvant trial, with 40% of these patients coming from Germany.

Trials with Lapatinib in the Neoadjuvant Setting

Since its first use in the early 1970s, neoadjuvant chemotherapy has become a standard of care for the management of locally advanced breast cancer and is increasingly used for the treatment of early breast cancer. The aims of neoadjuvant chemotherapy are i) downsizing of large tumors to improve resectability; ii) achievement of pathological complete remissions (pCR); and iii) providing information on the molecular biology of tumor responses to specific cytotoxic agents.

Fig. 3. Design of the NeoALTTO trial.

The meta-analysis of Mauri et al. [19], which includes 7 trials comparing adjuvant to neoadjuvant chemotherapy, showed no difference in recurrence-free and overall survival for patients receiving pre- or post-operative treatment. Based on study results, guidelines recommend several anthracycline- and taxane-containing chemotherapeutic regimens for the neoadjuvant therapy [11]. AC regimens followed by docetaxel and the TAC regimen with docetaxel/doxorubicin/cyclophosphamide are the most frequently recommended protocols. In patients with ErbB2-overexpressing breast cancer, trastuzumab can be applied as adjuvant therapy after tumor resection or concomitantly with the neoadjuvant chemotherapy. In the trial of Buzdar et al. [20], neoadjuvant therapy with paclitaxel, followed by the FEC (5-fluorouracil/cyclophosphamide/epirubicin) regimen plus trastuzumab, yielded significantly higher pCR rates than the same regimen without the monoclonal antibody.

The German GEPARDO studies have successively evaluated different treatment regimens containing doxorubicin and docetaxel in the neoadjuvant setting. GEPARQUINTO has the aim to optimize the preoperative treatment by incorporating different targeted agents into the neoadjuvant treatment strategy. This trial has a complex design with different settings for women with ErbB2-negative and -positive tumors and responding and non-responding patients. In the ErbB2-negative cohort, therapy consists of the EC (epirubicin/cyclophosphamide) regimen followed by docetaxel/capecitabine (DX), with or without the monoclonal anti-VEGF antibody bevacizumab. Non-responders to EC, i.e. chemoresistant patients, are switched to a less intensive and less toxic chemotherapy with paclitaxel with or without an mTOR inhibitor.

The ErbB2-positive cohort of the GEPARQUINTO trial aims at directly comparing trastuzumab and lapatinib, each in combination with the EC regimen followed by DX, in about 600 patients (fig. 2). In an interim analysis of the GEPARQUATRO trial, the simultaneous application of trastuzumab and the EC protocol showed promising results concerning car-

diotoxicity with no development of congestive heart failure in 100 evaluated patients [21]. Positive results with the combination of lapatinib and paclitaxel in the neoadjuvant treatment of inflammatory breast cancer have already been reported by Cristofanilli et al. [22]. Thus, the application of this TKI appears to be a reasonable strategy in the preoperative setting. Another approach to incorporate lapatinib into current neoadjuvant chemotherapy regimens will be investigated in the NeoALTTO trial: In 3 study arms, lapatinib, trastuzumab, or the combination of both anti-ErbB2 agents are administered preoperatively in combination with paclitaxel (fig. 3). After tumor resection, patients are treated with 3 cycles of the FEC regimen followed by the same anti-ErbB2 therapy as in the preoperative situation.

In conclusion, adjuvant chemotherapy has substantially improved the prognosis of breast cancer patients with a moderate or high risk of recurrence. In patients with ErbB2-overexpressing breast cancer, the development of agents targeted to this receptor led to an additional progress in clinical outcome. Trastuzumab was the first anti-ErbB2 drug successfully evaluated in the adjuvant setting. The availability of lapatinib, a dual TKI directed against 2 growth factor receptors, has the potential to mark another step forward in the treatment of early ErbB2-overexpressing breast cancer. Having two anti-ErbB2 drugs with different modes of action presumably offers the opportunity to increase efficacy by means of combination treatments and due to the availability of alternative strategies in the case of drug resistance.

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