

Lapatinib in the Treatment of Hormone Receptor-Positive/ErbB2-Positive Breast Cancer

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Key Words

ErbB2-positive breast cancer · Hormone receptors · ErbB2/ER pathway crosstalk · Endocrine resistance · EGF30008 trial

Summary

In women with estrogen receptor(ER)- and ErbB2 (HER2)-positive breast cancer, a vicious cycle is established between ER mechanisms of action and the growth factor receptor network, leading to enhanced cell proliferation and endocrine resistance. As such, co-targeting ErbB1 and ErbB2 with lapatinib in combination with hormonal therapy is an attractive approach to enhance the efficacy of either tamoxifen or estrogen deprivation. As demonstrated in the EGF30008 trial, a combined targeted strategy with letrozole and lapatinib significantly increased progression-free survival and clinical benefit rates in patients with metastatic breast cancer that co-expresses ER and ErbB2. Therefore, women who are not in an acutely life-threatening situation should be considered for upfront treatment with hormonal therapy (e.g. aromatase inhibitors) in combination with an anti-ErbB2 therapy.

Schlüsselwörter

ErbB2-positives Mammakarzinom · Hormonrezeptoren · ErbB2/ER-Pathway-Crosstalk · Endokrine Resistenz · EGF30008-Studie

Zusammenfassung

Bei Frauen mit Östrogenrezeptor- und ErbB2 (HER2)-positivem Mammakarzinom wird ein Circulus vitiosus zwischen den östrogenrezeptorvermittelten Wirkungen und dem Wachstumsfaktor-Netzwerk in Gang gesetzt, der in einer gesteigerten Zellproliferation und endokriner Resistenz resultiert. Daher ist eine gleichzeitig gegen ErbB1 und ErbB2 gerichtete Therapie mit Lapatinib ein attraktiverer Ansatz, um die Wirksamkeit einer antihormonellen Therapie zu steigern. Wie die Daten der EGF30008-Studie zeigten, lassen sich mit der kombinierten Gabe von Letrozol und Lapatinib bei Patientinnen mit metastasiertem Mammakarzinom und Östrogenrezeptor/ErbB2-Coexpression das progressionsfreie Überleben sowie der klinische Nutzen signifikant steigern. Daher sollte diese Kombination für Frauen, die sich nicht in einer akut lebensbedrohlichen Situation befinden, als Therapie der Wahl berücksichtigt werden.

Introduction

Co-expression of ErbB2 (HER2) and hormone receptors (HR) is a rather uncommon histopathological dualism: approximately half of ErbB2-positive breast cancers also express HR [1], accounting therefore for 10–15% of all breast cancer patients. It is generally accepted that women with HR-posi-

tive metastatic breast cancer should be treated with hormonal therapy as an initial treatment [2, 3]. However, in the ErbB2-positive patient population, early resistance is a significant issue with these endocrine agents [4]. Therefore, HR-positive tumors overexpressing ErbB2 still represent an important clinical problem and a major cause of treatment failure and mortality.

ErbB2/ER Pathway Crosstalk and Endocrine Resistance

Cumulative data from studies of estrogen receptor (ER) biology have identified a significant bidirectional crosstalk between the ER and growth factor-signaling networks, especially the ErbB2 signaling pathway. Estrogen has 2 known functional activities in breast cancer cells: in the classic genomic pathway, the hormone activates nuclear ERs, which leads to receptor phosphorylation, dimerization, and recruitment of co-activator proteins to the estrogen-bound receptor complex [1, 4]. In addition, there is also an activation of ERs located outside the nucleus in the cytoplasm and non-nuclear subcellular fractions. This so-called rapid non-genomic activity leads to phosphorylation, and as a result, activation of surface tyrosine kinase receptors such as the insulin-like growth factor I receptor (IGF-IR) as well as the ErbB2 receptor. This seems to be the site where the crosstalk between ER and growth factor receptors occurs. The molecular crosstalk between those two receptor systems is continuous and bidirectional, and the two systems are able to activate each other [1, 4].

Estrogen-deprivation therapies such as aromatase inhibitors (AIs) abolish genomic and non-genomic activities of ER and, therefore, could terminate the crosstalk generated in the presence of estrogen or tamoxifen in ErbB2-positive disease [1, 5, 6]. Data from preclinical models, however, suggest that resistance to estrogen-deprivation therapies in ErbB2-overexpressing breast tumors might occur through at least 2 mechanisms: adaptation to an estrogen hypersensitive phenotype and/or by ligand-independent recruitment of co-activator complexes to estrogen-responsive promoters [1, 7, 8].

Given the crosstalk activation, a treatment strategy of up-front dual targeting of both receptors with concurrent endocrine and anti-ErbB2 therapy appeared to be a logical approach to overcome or prevent endocrine resistance in patients with HR/ErbB2-positive tumors. Dual inhibitors of both ErbB1 and ErbB2 like lapatinib might be particularly suitable.

Preclinical Data of Co-Targeting ErbB1 and ErbB2 with Lapatinib

As shown in several preclinical studies, there is strong evidence that lapatinib may be effective in restoring tamoxifen sensitivity in HR-positive, tamoxifen-resistant breast cancer models. Chu et al. [9] demonstrated that lapatinib in combination with tamoxifen effectively inhibited the growth of tamoxifen-resistant, ErbB2-overexpressing MCF-7 mammary tumor xenografts. Leary et al. [10] showed greater antiproliferative effects for the combination of lapatinib with estrogen deprivation than either strategy alone in long-term estrogen-deprived and tamoxifen-resistant cells derived from parental hormone-sensitive MCF7 cells as well as in BT474 cells, a cell line with ErbB2 amplification and known sensitivity to lapat-

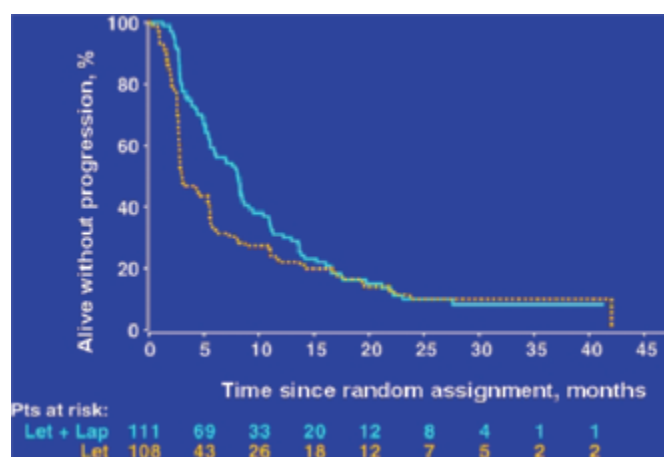


Fig. 1. Phase III EGF30008 trial: Kaplan-Meier estimates of progression-free survival, adapted from [11].

inib. Furthermore, the addition of lapatinib significantly enhanced the sensitivity to tamoxifen.

Clinical Evidence

Based on this preclinical evidence, the question of combined therapy has been addressed by the randomized, double-blind, placebo-controlled, multicenter phase III EGF30008 trial evaluating the effect of adding lapatinib to the AI letrozole as first-line treatment [11]. A total of 1,286 patients with ER-positive metastatic disease were randomly assigned to receive daily letrozole (2.5 mg orally) plus lapatinib (1,500 mg orally; $n = 642$) or letrozole plus placebo ($n = 644$); of these, 17% of patients in each arm had tumors centrally confirmed in a commercial laboratory as ErbB2-positive ($n = 111$ and $n = 108$, respectively). Baseline patient and disease characteristics were well balanced between treatment arms for both the ErbB2-positive ($n = 219$) and intention-to-treat HR-positive populations. As seen after a median follow-up time of 1.8 years, the addition of lapatinib to letrozole significantly increased the median progression-free survival (PFS) for HR/ErbB2-positive women ($n = 219$) from 3.0 months (letrozole-placebo) to 8.2 months, representing a statistically significant 29% reduction in the risk of disease progression (hazard ratio (HR) = 0.71; 95% confidence interval (CI) 0.53–0.96; $p = 0.019$) (fig. 1). Consistent with these findings, the overall response rate (ORR) in the ErbB2-positive population was significantly improved from 15 to 28% for patients treated with letrozole-lapatinib (odds ratio (OR) = 0.4; 95% CI 0.2–0.9; $p = 0.021$). Including patients with stable disease for ≥ 6 months, the clinical benefit rate (CBR) was likewise significantly improved (29 to 48%; OR = 0.4; 95% CI 0.2–0.8; $p = 0.003$). With less than 50% of overall survival (OS) events yet recorded, the median OS in the ErbB2-positive population was 32.3 months in the letrozole-placebo arm compared

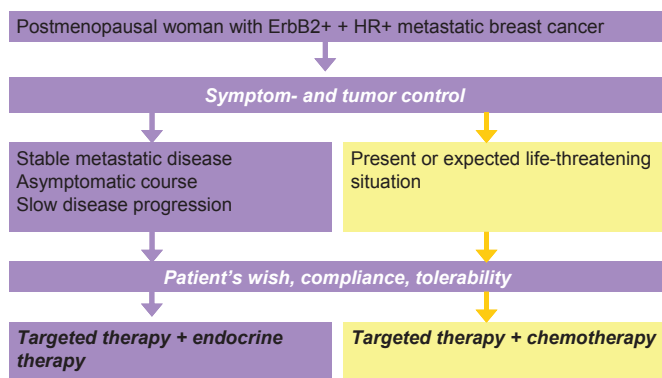


Fig. 2. Proposed therapeutic algorithm for the first-line therapy of women with HR/ErbB2-positive postmenopausal metastatic breast cancer.

with 33.3 months in the combination arm (HR = 0.74; 95% CI 0.5–1.1; $p = 0.113$). Grade 3 or 4 adverse events were more common in the lapatinib-letrozole arm versus the letrozole-placebo group (diarrhea 10 vs. 1%; rash 1 vs. 0%), but they were manageable. As the authors concluded, the EGF30008 trial demonstrated that a combined targeted strategy with letrozole and lapatinib significantly enhances PFS and CBR in patients with metastatic breast cancer that co-expresses HR and ErbB2.

Anti-ErbB2 Therapy Combined with Endocrine Therapy or Chemotherapy?

The combination of trastuzumab and chemotherapy offers a significant survival advantage when compared with chemo-

therapy alone for patients with ErbB2-positive breast cancer, regardless of HR status [12, 13]. On the other hand, patients have to tolerate the toxicities from the chemotherapy combination [12, 13].

Analogue to the therapeutic algorithm for ErbB2-negative patients in whom endocrine-based treatment or chemotherapy is depending on the number and site of the metastases, tumor growth dynamic, and life-threatening issues, the following therapeutic algorithm seems to be feasible when choosing a first-line therapy for women with metastatic HR-positive tumors overexpressing ErbB2 (fig. 2): combining chemotherapy with targeted therapy should be the first-line treatment option considered in patients with acute life-threatening disease. Patients who are not in an acute life-threatening situation should be considered for upfront treatment with hormonal therapy (e.g. AIs) in combination with an anti-ErbB2 therapy. As demonstrated in the EGF30008 trial (lapatinib + letrozole) [11] as well as in the TAnDEM trial (trastuzumab + anastrozole) [14], this is an appropriate approach to control patients for a significant period of time before chemotherapy (in combination with a targeted therapy) is required. Trastuzumab in combination with an AI is approved for this indication. The approval for lapatinib in combination with an AI is expected in 2010.

Disclosure Statement

The authors were speakers and contributors to the meeting 'ErbB2 (HER2)-positives Mammakarzinom; 2. Münchner Brustkrebs-Symposium Update 2009', 23/24 October 2009 in Munich, sponsored by GlaxoSmithKline.

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