Lapatinib in breast cancer

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Aberrant activation of some members of human epidermal growth factor receptor (HER) family plays a key role in breast carcinogenesis. Lapatinib is an oral dual tyrosine kinase inhibitor selective for inhibition of epidermal growth factor receptor (EGFR/ErbB1) and HER2/ErbB2. Having more targets, probably its antitumor activity could be more efficient. Clinical data have shown that lapatinib is active in HER2-positive breast cancer as monotherapy, in combination with trastuzumab, and in trastuzumab-resistant patients. Phase I clinical trials have shown also that lapatinib is well tolerated, with mild diarrhea and skin rash as common toxic effects and low incidence of cardiotoxicity. Phase II and III clinical trials' data provide encouraging evidence of the clinical effectiveness of lapatinib in advanced or metastatic breast cancer and for its potential in patients with brain metastases. Interim results from the large, phase III trial in 392 patients showed that in combination with capecitabine lapatinib almost doubled time to progression when compared with capecitabine alone. Several clinical trials that explore the efficacy of lapatinib in combination with conventional chemotherapeutic agents [paclitaxel (Taxol), capecitabine and platinoids], hormonotherapy and other target therapies are ongoing in advanced breast cancer or in neo-adjuvant and adjuvant settings. Our improved understanding of the biology of breast cancer and the use of biomarkers for identification of specific subtypes are allowing us to bring patient-specific novel therapies such as lapatinib to the clinic.

Key words: breast cancer, dual tyrosine kinase inhibitor, EGFR, GW572016, HER2, lapatinib

Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinases are involved in the regulation of normal and aberrant cellular proliferation and survival. This receptor subfamily is a group of four transmembrane receptors [EGFR/ErbB1, human epidermal growth factor receptor 2 (HER2)/ErbB2, HER3/ErbB3 and HER4/ErbB4] with extracellular domain (ECD) and intracellular tyrosine kinase activity. The activation of receptors is promoted by ligand-induced homo- and heterodimerization. Exceptions are represented by HER2, which has no known ligand, and HER3, which has no intrinsic tyrosine kinase activity. Dimerization induces receptor autophosphorylation and interaction with downstream mediators (Figure 1).

As HER2 is the only HER family receptor species that does not bind known ligands, its main biological role as a signal transducer results from recruitment into heterodimeric receptor complexes with ErbB1, ErbB3 and ErbB4 [1].

The type of partner in dimerization is important because it impacts on the downstream effect [2]. The members of Erb family are activated in many epithelial malignancies where they play a role in regulating tumor growth, survival and resistance to chemotherapy. Increased expression or constitutive activation of these receptor tyrosine kinases is associated with poor clinical outcomes.

Dysregulation of the HER-mediated signaling network has been implicated in the pathogenesis of breast cancer. Perhaps, the best example of this in human breast cancer is provided by the amplification of the HER2 gene, which results in HER2 protein overexpression. This alteration is present in ~20%–25% of human breast cancers and associated with significantly shortened disease-free survival and overall survival [3].

It has been indicated that HER2 may play an important role in the oncogenic activity of EGFR because preclinical experiments have shown that HER2 and EGFR act synergically to transform NIH3T3 cells [4].

Being the most common heterodimerization partner of EGFR [5], HER2 potentiates EGFR signaling by enhancing the binding affinity of its ligand EGF [6], reducing its degradation [7] and predisposing the receptor to recycling [8]. Moreover, it has been shown that EGF-induced stimulation of EGFR leads to activation of HER2 by transduction through heterodimerization [9], and recent studies have shown that EGFR-specific inhibitors can reduce HER2 signaling and growth of breast cancer cells that express high levels of HER2 [10–12]. Thus, combined inhibition of both EGFR and HER2 may be more effective than targeting each one [13].

The consequence of this consideration on the rule of receptor tyrosine kinases in promotion of cancer growth and survival is...
the therapeutic block of HER2 signaling by targeting either extracellular receptor sites with antibodies or abrogating HER2 autophosphorylation and receptor activation using small-molecule tyrosine kinase inhibitors [14]. Trastuzumab, a humanized monoclonal antibody (mAb) targeting HER2, induces G0/G1 cell cycle arrest in some models and apoptosis in other. However, the majority of patients receiving trastuzumab as a monotherapy do not have a clinical response. The question arising is whether combining a small-molecule HER2 tyrosine kinase inhibitor with anti-erbB-2 antibodies leads to enhanced tumor cell apoptosis since these two non-cross-resistant approaches target distinct sites on the HER2 receptor. A similar strategy was employed in HER1-expressing tumor cell lines, where combining cetuximab, an HER1 mAb, with either gefitinib or erlotinib, HER1 small-molecule tyrosine kinases inhibitors, leads to enhanced antitumor effects [14].

Lapatinib ditosylate monohydrated (GW572016; GlaxoSmith Kline, Research Triangle Park, NC) is an oral 4-anilinoquinazoline derivative that inhibits reversibly tyrosine kinase of HER1, HER2/ErBb2 and EGFR (dual tyrosine kinase inhibitor) (Figure 2). Like other small-molecule tyrosine kinase inhibitors, lapatinib competes with adenosine triphosphate for its binding site on the tyrosine kinase domain. Lapatinib binds the inactive form of EGFR and differs from other EGFR tyrosine kinase inhibitors, such as erlotinib or gefitinib, which bind EGFR in its active conformation. This explains why lapatinib has a slower dissociation rate compared with the other tyrosine kinase inhibitors, resulting in a greater duration of effect at the target site than that seen with either erlotinib or gefitinib [15].

The rational for development of dual EGFR/HER2 tyrosine kinase inhibitor, as opposed to a drug that targets only one member of the HER subfamily, is on the basis of several reasons. First, simultaneous inhibition of EGFR and HER2 may overcome redundancy in cell signaling pathways, a form of resistance observed in single tyrosine kinase inhibition in which upregulation of other members of the HER subfamily occurs [16].

Second, a dual EGFR/HER2 tyrosine kinase inhibitor may be useful in a wider range of patients due to findings implicating the role of EGFR and HER2 heterodimer formation in the progression of a variety of cancer types. Third, synergistic inhibition of cancer cell growth has been demonstrated with simultaneous targeting of EGFR and HER2, resulting in more potent inhibition in cell growth compared with targeting either EGFR or HER2 alone [13, 17].

**pharmacology and preclinical studies**

*In vitro* studies, lapatinib, have revealed cell growth inhibition and apoptosis induction in various human cancer cell lines (head and neck, lung, breast, gastric, vulva). This is the effect of a dose- and time-dependent reduction of phosphorylation of EGFR and HER2 and their downstream effectors, Akt, implicated in cell survival and mitogen-activated protein kinases (Erk1/2) involved in cell proliferation. Potency and selectivity in *vitro* were found to have 50% inhibitory concentration (IC50) values against purified EGFR and HER2 of 10.8 and 9.3 nM, respectively [18]. Compared with other EGFR-selective tyrosine kinase inhibitors such as gefitinib and erlotinib, lapatinib had a slower dissociation of its target site resulting in prolonged receptor down-regulation [15].

*In vivo* lapatinib caused dose-dependent inhibition of human tumor xenograft growth (GEO colon cancer, HN5 head and neck cancer and BT474 breast cancer), and indicated that lapatinib may be an effective therapy for EGFR- or HER2-overexpressing tumors in patients [18, 19]. The effect of lapatinib either alone or in combination with other therapies has been tested in various human breast cancer cells.

In murine mammary xenografts of estrogen receptor (ER)-positive, tamoxifen-resistant breast tumors, lapatinib is able to restore tamoxifen sensitivity. The combination of lapatinib and tamoxifen leads to a more rapid and profound antiproliferative effect than with either of the drugs on their own [20].

In breast cancer cells that overexpress a truncated but activated form of HER2 (p95erbB2), HER2 preferentially forms heterodimers with HER3 and is regulated by heregulin (a HER3 ligand) and not EGF [21]. As such, the HER2-positive cells were resistant to the mAb trastuzumab, but sensitive to lapatinib. Separate studies have indicated that combining lapatinib with anti-HER2 antibodies may produce synergistic effects and enhance apoptosis in HER2-overexpressing breast cancer cells [22].

In breast cancer cell line, lapatinib have demonstrated a radiosensitizing effect mediated through EGFR signaling, that
involved Ras, which may be useful in overcoming radioresistance [23–25].

Preclinical data provided the biological rationale to evaluate lapatinib clinically, both as single agent and in combination with tamoxifen or trastuzumab in breast cancer patients [20, 26].

**pharmacokinetic and phase I studies**

Oral administration of drug in healthy human volunteers and patients with cancer demonstrated the tolerability of lapatinib with no severe adverse events [27–29]. The common side-effects reported included diarrhea, rash, nausea, vomiting and headache. The absorption from the gastrointestinal tract was constant, and dose-dependent serum concentration peaked 3–4 h after dosing. The half-life was ~17 h with achievement of steady-state concentration after 6–7 days of o.d. dosing, with elimination via first-pass metabolism catalyzed by CYP3A4/5 enzyme and does not appear to be a substrate for P-glycoprotein [28, 30].

The safety and maximum tolerated dose of lapatinib have been evaluated in a variety of phase I study.

Pandite et al. in EGF10003 study explored the maximum tolerated dose of lapatinib in 81 heavily pretreated metastatic cancer patients who were not selected on the basis of EGFR or HER2 receptor status. Patients were treated with lapatinib on an o.d. or b.i.d. continuous schedule. O.d. doses ranged from 175 to 1800 mg and b.i.d. doses were 500, 750, and 900 mg per dose. In 64 patients who were assessable for safety and tumor response lapatinib on a schedule o.d. was well tolerated at all dose while 50 and 750 mg b.i.d. were better tolerated than 900 mg b.i.d. There were no grade 4 toxic effects and a dose-limiting toxicity (DLT) was not observed. The majority of adverse events were grade 1 or 2 skin, transient diarrhea, nausea, fatigue and anorexia, manageable with symptomatic treatment. One patient with head and neck cancer achieved complete response (CR) and 22 patients had a stable disease (SD) [31].

In EGF10004 study, 67 patients with metastatic solid tumors, that overexpressed HER1 and/or HER2, were enrolled to receive lapatinib at doses ranging from 500 to 1600 mg o.d. Lapatinib was well tolerated. The clinical activity was observed in the range of doses 650–1600 mg daily. The most frequent drug-related adverse events were diarrhea (42%) and rash (31%). No grade 4 drug-related adverse event, pneumonitis, or cardiac dysfunction was reported. Five grade 3 drug-related toxic effects (gastrointestinal events and rash) were experienced by four patients. A DLT was not observed. Four patients with trastuzumab-resistant metastatic breast cancer had a partial response (PR). Twenty-four patients with various other carcinomas experienced SD, of whom 10 received lapatinib for ≥6 months.

Furthermore, analysis of dose and concentration relationship with response determined that the majority of responders were receiving 1200 mg of lapatinib per day and had a serum through concentration of 0.3–0.6 µg/ml [30].

Lapatinib was combined with biologic and chemotherapeutic agents [trastuzumab, paclitaxel (Taxol), capecitabine and platinoid] in several phase I study.

A phase I/II study involving only patients with metastatic breast cancer examined the effects of lapatinib in combination with trastuzumab [32]. In total, 22% of patients achieved a CR or PR and 37% had SD.

**Lapatinib in breast cancer: phase II and III studies**

Two nonrandomized, open-label, multicenter, phase II clinical trials were conducted to assess the safety and efficacy of lapatinib monotherapy for metastatic breast cancer refractory to either trastuzumab or anthracyclines, taxanes and capecitabine. These studies indicated activity of lapatinib in trastuzumab-prefertated patients.

In the EGF20002 study were enrolled 78 patients with HER2-overexpressing metastatic breast cancer, with progressive disease on prior trastuzumab-containing regimens. Patients received lapatinib daily at a dose of 1500 mg.

In EGF20008 study were selected two cohort of patients. Cohort A included 140, HER2-overexpressing trastuzumab-refractory metastatic breast cancer patients, cohort B included 89, HER2 nonoverexpressing metastatic breast cancer with no prior trastuzumab. In the preliminary analysis, 22% of EGF20002 and 14% of EGF20008 patients obtained a response (CR, PR, SD) [33]. The responses were restricted at HER2-positive patients. A combined biomarker analysis was conducted in both studies to determine the correlation between clinical parameters, tissue/serum biomarker expression and response to lapatinib. Using standard Immunohistochemistry (IHC) techniques, tumors were stained for EGFR family (erbB1-4), IGF1R, truncated erbB-2 (p95), heregulin and p-Erk 1/2, ER and PgR. Sequential quantitation of ECD of EGFR and HER2 was obtained. Initial data indicated that ER, PgR negativity and erbB-1 overexpression and an intact ECD of HER2 may be related to lapatinib resistance in trastuzumab-prefertated patients.

In EGF103009 study, a phase II international multicenter trial, patients with relapsed/refractory inflammatory breast cancer (IBC) received single-agent lapatinib at doses of 1500 mg/day; tumor expression of ErbB2, p-ErbB2, ErbB1, p-ErbB3, IGF-1R, PTEN, ER/PgR, E-cadherin, β-catenin and Rho B/C was analyzed. The study accrued 58 patients who were divided in two cohorts, cohort A (erbB2 overexpressors: 2/3 IHC/FISH+) and cohort B (erbB1/2 non-overexpressors). Initial results were reported on 36 patients. A 62% PR rate was seen in cohort A, 21% had a SD. In cohort B, 8% of patients had a PR and 17% had a SD. All responders overexpressed ErbB2, increased p-ErbB2, coexpressed IGF-1R and expressed activated p-ErbB1 [34]. Coexpression of IGF-1 and HER2 has been indicated as a potential mechanism of resistance to trastuzumab [35]. In fact, 75% of the patients in cohort A were refractory or resistant to trastuzumab. This study indicates sensibility to lapatinib and provides an interesting biological definition of IBC. ErbB2 overexpression but not ErbB1 expression, p-ErbB2 and IGF-1R coexpression predict for sensitivity to lapatinib in IBC.

Gomez et al. evaluated lapatinib efficacy in first-line advanced or metastatic breast cancer setting. In the
EGF20009, a phase II randomized, study, patients with HER2 amplification, FISH documented, were randomly assigned to receive oral lapatinib as either a o.d. dose of 1500 mg, or 500 mg b.i.d. The planned number of patients was 130. An interim analysis is available on 40 patients. By independent radiology review, 35% of the patients had PR and a further 5% had unconfirmed PRs; 35% of the patients had a SD [36].

Lin et al. explored, in a phase II trial, the role of lapatinib in new or progressive brain metastases from breast cancers overexpressing erbB2. Patients received oral lapatinib at a dose of 750 mg b.i.d. The primary end point was objective response. Thirty-nine patients were enrolled. All patients developed brain metastases during treatment with trastuzumab, 38 progressed after prior radiation therapy. Two patients (5%) achieved a PR and remained on study for 158 and 347 days. Eight patients had SD in the central nervous system (CNS) at 16 weeks. The three-dimensional evaluation of tumor size showed more promising result than conventional RECIST [37]. The volumetric decline in CNS lesions correlated with improvements in quality of life.

Recently turned out to be published by Geyer et al. [38] the results of EGF100151, the first large phase III trial comparing lapatinib in combination with capecitabine versus capecitabine alone in women with advanced, progressive HER2-positive breast cancer heavily pretreated with anthracycline, taxanes and trastuzumab. Patients were randomly assigned to receive either oral lapatinib (1250 mg o.d. for 14 consecutive days, with 1 week rest) in combination with oral capecitabine (2000 mg/m² per day for 14 consecutive days, with 1 week rest) or single-agent capecitabine (2500 mg/m² per day for 14 consecutive days, with 1 week rest). Both treatments were planned to be administrated until tumor progression or unacceptable toxicity. The primary end point was time to progression (TtP), and secondary end points were overall survival, progression-free survival, response rate, clinical benefit response (CBR) and toxicity. The study was closed at first interim analysis when 321 patients were accrued. The interim analysis showed that the addition of lapatinib to capecitabine was associated with a 51% reduction in the risk of disease progression (hazard ratio 0.51, \( P = 0.00016 \)). The median progression-free survival time was 37 weeks, compared with 18 weeks for those in the capecitabine single-agent arm (\( P = 0.000045 \)). The overall response rate was 23% in combination therapy group and 14% in monotherapy group (\( P = 0.113 \)). The combination therapy group experienced less progressive CNS metastases (11 versus 4), but the difference was not statistically significant (\( P = 0.10 \)).

Both treatment arms were well tolerated with similar discontinuation as a result of adverse events (14% in combination group versus 11% in monotherapy group). The main difference in the toxicity profile was an increase in grades 1 and 2 diarrhea in the combination group (45% versus 28%). In the combination arm, four patients experienced cardiac events that were treatment related and fully recovered, whereas one patient in the capecitabine monotherapy group experienced a cardiac event unrelated to treatment, which remained unresolved.

Several clinical trials that explore the efficacy of lapatinib in combination with chemotherapy, hormonotherapy and other target therapies are ongoing or starting in advanced breast cancer setting.

Lapatinib is potentially an ideal therapy for the adjuvant treatment of breast cancer because it has shown activity in the first-line and refractory metastatic settings with mild toxic effects and decreased incidence of brain metastases. Some trials, as Tyrkeb Evaluation After Chemotherapy or Adjuvant Lapatiniband/or Trastuzumab Treatment Optimization, are ongoing to investigate adjuvant rule of lapatinib.

**lapatinib cardiotoxicity**

Targeting HER2 with mAb or small molecule was potentially cardiotoxic. Perez et al. [39] reviewed the cardiotoxicity data of lapatinib in 3558 patients, including 1674 breast cancer patients, already treated with the drug alone or in combination with other agents. A total of 1090 patients had ≥6 months exposure to lapatinib. Evaluation of cardiac left ventricular ejection fraction (LVEF) was done every 8 weeks while patients were receiving therapy, in addition to follow-up for any cardiac clinical events. A preliminary analysis of patients treated with lapatinib to date revealed that incidence of symptomatic and asymptomatic decreased LVEF among 1674 breast cancer patients was 1.3% and was also 1.3% among 1453 patients with nonbreast malignancies. Lapatinib-associated LVEF decrease was symptomatic in 0.1%, generally reversible/nonprogressive. Average duration of LVEF decrease was 40 days. Further patient follow-up is ongoing.

**conclusion**

Lapatinib (GW572016) is an oral dual tyrosine kinase inhibitor selective for inhibition of EGFR/ErbB1 and HER2/ErbB2. This small molecule represents one of the most promising target therapies in breast cancer that overexpressed HER2. The activity in refractory metastatic breast cancer and in first-line metastatic treatments, with potential benefit in patients with brain metastases, has generated substantial enthusiasm among oncologists for the drug. Interim results from a large, phase III trial in 392 patients showed that in combination with capecitabine, lapatinib almost doubled TtP when compared with capecitabine alone. Several clinical trials that explore the efficacy of lapatinib in combination with conventional chemotherapeutic agents (paclitaxel, capecitabine and platinoids), hormonotherapy and other target therapies are ongoing in advanced breast cancer or in neo-adjuvant and adjuvant settings. Our improved understanding of the biology of breast cancer and the use of biomarkers for identification of specific subtypes are allowing us to bring patient-specific novel therapies such as lapatinib to the clinic.

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