LAPATINIB IN BREAST CANCER – THE PREDICTIVE SIGNIFICANCE OF HER1 (EGFR), HER2, PTEN AND PIK3CA GENES AND LAPATINIB PLASMA LEVEL ASSESSMENT

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Background. Breast cancer treatment trends are currently based on tailored therapies using tumor and patient biomarkers. Lapatinib is the first dual inhibitor of HER1 (EGFR, ErbB1) and HER2 (ErbB2, Neu) tyrosine kinases to be used in clinical practice. However, only HER2 is currently used for therapy indications and new predictors for the treatment with lapatinib are sought.

Methods and results. This minireview focuses on lapatinib and its role in breast cancer treatment. Preclinical and clinical studies as well as pharmacological characteristics are briefly reviewed while the focus is on efficacy assessment including predictive factors for therapy outcome.

Conclusion. Lapatinib (Tykerb/Tyverb) was Food and Drug Administration (FDA) approved in 2007 for use in combination with capecitabine for the treatment of HER2-positive advanced or metastatic breast cancer in patients who had received previous treatment (including anthracycline, taxane and trastuzumab containing regimens) and in 2010 for use in combination with letrozole for postmenopausal women with hormonal receptor positive and HER2-positive metastatic breast cancer. In contrast to trastuzumab (Herceptin), lapatinib is orally administered and it targets both HER2 and HER1 receptors. As a synthetic and oral tyrosine kinase inhibitor (TKI), it is convenient, cheaper and easier to produce than monoclonal antibodies. The recommended dosage is not dependent on body weight either. Lapatinib plasma level measurement could be an approach to tailored therapy for further optimizing the dose and prolonging this efficient therapy. New lapatinib response predictors are being evaluated. At this time, only HER2 amplification/overexpression is used to choose lapatinib therapy candidates. Further studies on concurrent HER1 fluorescent in situ hybridization (FISH)/immunohistochemistry (IHC) assessment and/or microarray analyses may produce new data on the predictive role of the HER1 (EGFR) gene/protein. PTEN loss and PIK3CA gene mutations are other markers that may predict lapatinib poor response.

INTRODUCTION

Breast cancer (BC) is the most common malignancy in females affecting around 1.3 million women worldwide each year and causing about 460,000 deaths annually. Data from the Czech National Oncology Registry indicate that the incidence of BC has doubled since 1977 and in 2007 BC affected 123.2/100,000 women with a mortality of 31.9/100,000 (ref.). Metastatic breast cancer (MBC) is found at initial diagnosis in up to 10% of patients. Tailored therapy based on biological markers of tumor and patient is the trend in clinical practice these days. Lapatinib (Tykerb/Tyverb, GlaxoSmithKline, Research Triangle Park, NC) was introduced into routine clinical settings and follows success of hormonal therapy (used in hormonal receptor positive BC) and the monoclonal antibody trastuzumab (Herceptin, Genentech, South San Francisco, CA) indicated in HER2 overexpressed and/or amplified breast cancers. This minireview focuses on lapatinib in BC treatment. Preclinical and clinical studies as well as pharmacological characteristics are briefly reviewed while the focus is on efficacy assessment including predictive factors for therapy outcome.

THE HER FAMILY AND ITS BLOCKADE

The family of cell receptors called human epidermal growth factor receptors (HER) plays an important role in tumor development via influence on cell proliferation, migration, angiogenesis and protection against apoptosis in many cancer types. The HER family consists of four
members – HER1 (also known as epidermal growth factor receptor, EGFR), HER2, HER3 and HER4. These receptors are composed of an N-terminus extracellular ligand-binding domain, a single membrane spanning region and a C-terminus cytoplasmic domain which exhibits tyrosine kinase activity. However, HER2 has no known ligand and HER3 lacks tyrosine kinase activity. After ligand binding on extracellular domains, receptors homo- or heterodimerize and become active through autophosphorylation. This activation allows further signal transduction. The intracellular downstream signal is split into two important pathways: the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K)-Akt pathways.

Two main approaches are used in cancer therapy to block membrane receptors and thus their signaling – via monoclonal antibodies or blocking kinase activity using small molecules - TKIs. Monoclonal antibodies are intravenously administered. They bind the extracellular domain of the receptor, inhibit signaling and attract immune response. On the other hand, TKIs are orally administered small molecules targeting the intracellular part of the receptors. In the case of BC, both approaches are used in clinical practice. Both trastuzumab, and lapatinib, have been approved by the FDA and the European Medicines Agency (EMEA) for BC treatment. Lapatinib (Tykerb/Tyverb) was FDA approved in 2007 for use in combination with capecitabine for the treatment of HER2-positive (HER2+) advanced or MBC in patients who had received previous treatment (including anthracycline, taxane and trastuzumab containing regimens) and in 2010 it was approved in combination with letrozole for postmenopausal women with hormonal receptor positive and HER2+ MBC.

TKIs are cheaper and easier to produce than monoclonal antibodies. As they are taken orally this is a great advantage to cancer patients, 83-92% of whom prefer this form of administration according to various studies.

**Lapatinib – mechanism of action**

Lapatinib (GW572016) was derived from the quinazoline core found to be active in other HER TKIs. Its chemical name is N-[3-chloro-4-[(3-fluorobenzyl)oxy]phenyl]-6-[5-[(2-methylsulfonyl)ethyl] amino [methyl]-2-furyl]-4-quinazolinamine. It has been shown to inhibit the intracellular domain phosphorylation of both HER2 and HER1 in a reversible manner with a long dissociation time of receptor-drug complex estimated as ≥ 300 min. The described effect is due to the lapatinib structure and its ability to bind at an ATP binding site in inactive form.

In humans, lapatinib is administered as the monohydrate ditosylate salt. The specificity of lapatinib has been tested on a wide range of protein kinases. An affinity was found only for HER4 and e-Src apart, that is from HER2 and HER1. Lapatinib blocks, by inhibition of HER2 and HER1, activation of subsequent intracellular pathways leading through extracellular signal-related kinase (ERK)-1/2 and PI3K/Akt. Lapatinib can inhibit both wild-type and truncated forms of HER2 receptors (p95HER2) both in vitro and in vivo.

**In vitro and xenograft studies**

Rusnak et al. showed growth inhibition of tumor cells overexpressing both receptors – HER1 (head and neck cancer, vulvar cancer cell lines) and HER2 (breast, gastric, lung cancer cell lines). The ability of lapatinib to inhibit the proliferation of tumor cells overexpressing HER1 was compared with erlotinib and a similar impact on growth was found. Inhibition of HER1 and HER2 receptor autophosphorylation and phosphorylation of the downstream modulator, Akt, was verified by Western blot in the BT474 and HN5 cell lines. HER1 and HER2 receptor autophosphorylations were similarly inhibited by lapatinib. However the level of Akt phosphorylation was, post-treatment, lower in HER2+ samples than in HER1 positive samples. In proliferation and cell cycle assays, lapatinib proved to be more effective against HER2-overexpressing cell lines than against HER1-overexpressing cell lines. However these results might be due to the specific cell lines used. The results suggest that HER1 inhibition leads preferentially to cell growth arrest and HER2 inhibition causes both growth arrest and cell death after 72 h in vitro. The authors also confirmed that lapatinib was capable of inhibiting the growth of human tumor cells in vivo, using HN5 and BT474 xenograft models. Taken together, these results indicate that lapatinib achieves excellent potency on tumor cells with selectivity for tumor versus normal cells and they suggest that lapatinib would benefit patients with tumors overexpressing either HER1 or HER2. Another study showed potent inhibition of both HER1 and HER2 tyrosine kinases leading to growth arrest and/or apoptosis in HER1 and HER2-dependent tumor cell lines as a response to lapatinib treatment. Lapatinib markedly reduced tyrosine phosphorylation of both HER1 and HER2, and inhibited activation of Erk1/2 and Akt. However, the inhibition of phosphorylated (p)-Akt in HN5 cells overexpressing HER1 was smaller than in HER2-overexpressing tumor cells. Lapatinib inhibited activation of HER1, HER2, Erk1/2 and Akt in human tumor xenografts as well. Lapatinib efficacy both in vitro and in vivo was also confirmed by Konecny et al.

**Clinical studies**

Phase I clinical studies have proven the safety of lapatinib administration either alone or in combination with another oral agent, capecitabine. In the phase I study of Burris et al., out of 67 patients with advanced solid tumors displaying HER1 expression by immunohistochemistry (IHC) and/or HER2 overexpression by IHC or amplification by fluorescence in situ hybridization (FISH) 30 (44.7%) were treated for BC. Patients who experienced complete remission, partial response (PR) or stable disease in the phase I studies were mainly those suffering from BC. The phase II study in HER2+ MBC patients after trastuzumab treatment failure, produced more results supporting the safety of lapatinib and it evaluated its benefits. Lapatinib demonstrated modest activity as a single agent. A combination of capecitabine and lapatinib significantly prolonged treatment efficacy with acceptable toxicity.
tion showed better response to lapatinib with capecitabine than capecitabine alone in a group of HER2+ BC patients suffering from locally advanced or metastatic disease. Lapatinib also inhibited truncated forms of HER2 receptor (p95HER2) in BC patients, partially explaining its activity in trastuzumab resistant disease. The development of CNS metastases is a serious clinical problem occurring in approximately one third of women with MBC who receive trastuzumab. The phase II studies using lapatinib in BC with brain metastases showed volumetric changes in the metastases. Lapatinib plus capecitabine resulted in 20% CNS objective response and in 40% a ≥ 20% volumetric reduction in their CNS lesions was observed. More recently, other studies on lapatinib in combinations have been published: with trastuzumab, paclitaxel and hormonal treatment, some also in neoadjuvant settings. One study exploring the combination of anthracycline-based chemotherapy plus trastuzumab, lapatinib, or both in a neoadjuvant setting is ongoing. Important and relevant outcomes are expected from an international ALTTO phase III adjuvant trial that will evaluate 8,000 early HER2+ BC patients and will produce data on lapatinib and trastuzumab in combination, both alone and in sequence. The first patient was enrolled in 2007. BC patients will receive study treatment for one year, and will be followed for a total of 10 years.

**Pharmacokinetics**

**Absorption:** Lapatinib is a small orally administered molecule, whose absorption depends on concurrent conditions. Detectible levels of lapatinib are found in the blood after 0.25 hours ranging from 0 to 1.5 hours with the maximum concentration reached approximately after 3 to 4 hours. A daily dose of 1,250 mg causes steady state levels of Cmax 2.43 mcg/ml (1.57 to 3.77 mcg/ml) and the area under the curve (AUC) 36.2 mcg.hr/ml (23.4 to 56 mcg.hr/ml). With multiple daily dosing, a steady state was achieved within 6 to 7 days. Lapatinib is bound (>99%) to albumin and alpha-1 acid glycoprotein in the blood stream but it does not undergo erythrocyte binding which creates a blood to plasma ratio <1. In vitro studies have shown that lapatinib is a substrate for and inhibitor of P-glycoprotein (Pgp). The metabolism depends primarily on CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 followed by biliary elimination and stool excretion. Renal excretion accounts for less than 2% of the given dose. The elimination t1/2 was 14.2 hours after a single dose administration, and 24 hours with repeated dosing (result of drug accumulation). In patients with severe hepatic dysfunction (Child-Pugh class C), the AUC of lapatinib was increased by >60% and the t1/2 was 3 times that of individuals without hepatic disorder. Thus, dose reductions to 750 mg/d are recommended in patients with liver disease. Ketoconazole, a CYP3A4 inhibitor, increases the AUC of lapatinib and t1/2. The package insert recommends avoidance of strong CYP3A4 inhibitors. If co-administration is necessary, reduction of the lapatinib dose to 500 mg/d is advised. On the other hand, carbamazepine, a CYP3A4 inducer, decreases the AUC of lapatinib. Avoidance of strong CYP3A4 inducers is recommended, and if it is necessary to receive a strong CYP3A4 inducer in combination with lapatinib, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2 positive MBC indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor positive, HER2+ BC indication) based on tolerability as recommended by the FDA. However, there are no published clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers.

**Resistance to lapatinib**

As a small tyrosine kinase molecule, lapatinib affects receptors and signal transduction at a different level than trastuzumab. Moreover, different modes of cellular drug resistance have been suggested for trastuzumab and lapatinib and this underlines the rationale of lapatinib administration after trastuzumab failure. However, some BCs do not respond or develop resistance to lapatinib too (e.g. tumors with HER2 tyrosine kinase domain mutations; HER1 tyrosine kinase domain mutations; PIK3CA mutation, PTEN loss, AXL overexpression, ReLA activation). Enhanced estrogen signaling described in vitro may also be a route for increased tumor cell survival on lapatinib treatment. Combining lapatinib treatment with fulvestrant reduced the rate of lapatinib resistance. One in vitro study has shown AXL overexpression as a novel mechanism of acquired resistance to HER2-targeted agents, which can be overcome by a new multikinase (AXL, MET, and VEGFR) inhibitor foretinib. Further, AXL expression in vitro was also decreased using small interfering RNA to AXL, estrogen deprivation or estrogen receptor antagonist fulvestrant and, sensitivity to lapatinib was restored. These findings also suggest that epigenetic changes may play a role in lapatinib resistance. Taken together, the results support the use of different targeted therapeutics in combination.

**Treatment tailoring and efficacy**

Response to lapatinib administration may be influenced both by tumor and patient characteristics. The tumor phenotype, predictor status, drug dose as well as other factors may play a role here. Lapatinib has been proven to be more absorbed by a high-fat diet. The following steps of lapatinib body passage depend on liver metabolism and cytochrome inducers/inhibitors. The level of proteins in blood available to bind lapatinib may also be a route for increased tumor cell survival on lapatinib treatment. Combining lapatinib treatment with fulvestrant reduced the rate of lapatinib resistance. One in vitro study has shown AXL overexpression as a novel mechanism of acquired resistance to HER2-targeted agents, which can be overcome by a new multikinase (AXL, MET, and VEGFR) inhibitor foretinib. Further, AXL expression in vitro was also decreased using small interfering RNA to AXL, estrogen deprivation or estrogen receptor antagonist fulvestrant and, sensitivity to lapatinib was restored. These findings also suggest that epigenetic changes may play a role in lapatinib resistance. Taken together, the results support the use of different targeted therapeutics in combination.
THE HER FAMILY

The HER1 gene is located on 7q12 and its protein product plays an important role in cell proliferation, migration and protection against apoptosis\(^1\). In contrast, to HER2, overexpression of HER1 appears to be a later event in tumorigenesis\(^2\). Increased HER1 protein expression is described in about 40% of BC, (ranging from 14% to 91% of all primary BC)\(^3\). High expression is described in triple negative breast cancer and metaplastic cancer to 91% of all primary BC. HER1 overexpression was found in 30% of inflammatory breast cancer (IBC). Patients with HER1-positive tumors have worse 5-year overall survival than patients with HER1-negative tumors, and HER1 expression is associated with an increased risk of recurrence in patients with IBC\(^4\). The HER1 gene was amplified in a nonselected series in 0-14%, in metaplastic cancer up to 28% (ref.\(^5\)). In a study by Reis-Filho et al.\(^6\), which assessed 47 metaplastic cancers, HER1 amplification showed a significant association with HER1 overexpression and was restricted to cancers with homologous metaplasia. Coexpression of HER1 and HER2 has been observed in 10-36% primary BC, and it is associated with a poorer prognosis than in cases with expression of a single receptor\(^7\). In one study, where HER1 expression was found in only 15% of 807 invasive BC, the majority of HER1-positive tumors (87%) coexpressed HER2. Moreover, almost all the tumors that expressed the HER2 phosphorylated form (pHER2), coexpressed HER1, and expression of pHER2 or coexpression of HER2 and HER1 was associated with the shortest patient survival\(^8\). The HER2 gene is localized in the 17q12-q21 amplicon and its amplification occurs in approximately 20-35% of invasive BC\(^9\). HER2 overexpression/amplification is widely accepted as a lapatinib therapy response predictor based on the results of several clinical studies\(^10,11,12\). Coexpression of pHER2 and pHER3 in IBC seems to predict a favorable response to lapatinib even more accurately\(^13\). On the other hand, HER1 did not predict lapatinib response in various studies\(^14,15,16\). However, HER1 protein was assessed using IHC but no HER1 gene examination by FISH was performed\(^17,18,19\). In another study, additional correlative tumor tissue analyses including HER1 were conducted, but the small number of responders precluded any useful interpretation of these results\(^20\). Further, the HER1 status was not published in some studies\(^21,22\). In a phase I study of 67 patients with metastatic solid malignancies and using 6 different lapatinib doses ranging from 500 to 1,600 mg/d, 59 patients were assessed for treatment results. Breast cancer presented in 15 out of 33 patients with assessed biomarkers. Four PR were observed: these were all in BC and all of them overexpressed HER2 at 3+ level by IHC and three also displayed HER1 expression. HER1 IHC results were described as positive or negative\(^23,24\). Detailed receptor status evaluation showed PR in patients with high HER2 activated level. Lapatinib treatment lowered both HER2 and HER1 phosphorylation but did not change overall receptor expression\(^25\). In a phase II study, HER2 overexpression but not HER1 expression alone, predicted sensitivity to lapatinib in BC; high HER2, pHER2 and insulin-like growth factor receptor-1 (IGF-IR) coexpression predicted clinical response to lapatinib monotherapy in patients with relapsed/refractory IBC\(^26\). In a phase III study, investigators revealed the low frequency of HER1 IHC 2+ or 3+ overexpression (44/320, 14% in both arms, 25/163, 15% in patients treated with lapatinib+capecitabine and in 19/157, 12% treated with capecitabine) in the available tumor specimens. The results suggested that HER1 overexpression did not play a significant role in the biology of the HER2+ BC of women included in this trial. The authors were unable to identify a subgroup of patients who fail to benefit from the addition of lapatinib to capecitabine based on the biomarker studies. There was no association identified between level of HER1 expression and progression-free survival (PFS)\(^27,28\). Burstein et al.\(^29\) found no correlation between HER1 expression level assessed via IHC and response to lapatinib (six patients had an objective response to lapatinib by investigators review, two by independent review). Combined biomarker analysis was performed by Blackwell et al.\(^30\) in two large phase II studies with refractory MBC and they published initial data suggesting that expression levels of estrogen, progesterone and HER1 receptors may be related to lapatinib response in trastuzumab pretreated patients. Tumor tissues were obtained from each patient from the time of most recent biopsy. Phase II study EGF20009 assessed lapatinib as first line monotherapy in advanced or metastatic BC and for the initial 65 patient samples analyzed, an elevation of HER2 expression was significantly associated with response to treatment with lapatinib (p=0.02) and a longer time to progression following treatment with lapatinib (p<0.0025). Further, of the 17/65 responders in this preliminary study, SpotFire\(^31\)Decision Tree Analysis demonstrated that 16/17 (94%) who responded to lapatinib had a gene expression signature combining HER1, 2, and 3 (ref.\(^32\)). Further large studies focusing on concurrent HER1 FISH/IHC assessment or microarray analyses on samples from metastatic sites if available could produce new data on the predictive role of this marker. Comparison of HER1 gene/protein status in primary and metastatic sites may also be a tool to better assess the role of HER1 receptor in BC patients.

PIK3CA

Activation of the phosphoinositide 3-kinase (PI3K) pathway plays an important role in the pathogenesis of a variety of cancers. The gene encoding the p110alpha catalytic subunit of PI3K (PIK3CA) can be mutated in up to 40% of BC. The majority of PIK3CA mutations lie in two hotspot regions, including the central helical domain encoded by exon 9 and the COOH-terminal kinase domain encoded by exon 20(ref\(^33\)). The PIK3CA activating mutations (E545K and H1047R) cause resistance to lapatinib\(^34\). Patients with tumors harboring an H1047R PIK3CA mutation or low expression of PTEN, derived clinical benefit from lapatinib in one phase II study\(^35\).
On the other hand, PIK3CA mutations have recently been found to sensitize cancer cells (with KRAS/BRAF normal status) to the mammalian target of the rapamycin (mTOR) inhibitor everolimus. Clinical trials testing mTOR inhibitors are currently ongoing, and this includes BC patients. Taken together, PIK3CA mutations may serve as both positive (mTOR inhibition) and negative (lapatinib) therapy predictors in BC.

PTEN

The phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a tumor suppressor identified in 1997 in the 10q23 region. PTEN phosphatase negatively regulates the PI3K pathway and is inactivated in many human malignancies, including BC. However, there are no uniform study results. Knockdown of PTEN did not alter response to lapatinib in vitro and PTEN loss was not associated with reduced response to lapatinib in a phase II monotherapy trial in IBC, as approximately 70% of responders showed PTEN deficiency. Patients with tumors harboring an H1047R PIK3CA mutation or low expression of PTEN derived clinical benefit from lapatinib in one phase II study. On the other hand, a combined in vitro and in vivo study using a genome wide loss-of-function short hairpin RNA (shRNA) screen identified loss of PTEN expression as one of causes of lapatinib resistance. Recently, a distinct resistance mechanism has been proposed. PTEN inactivation specifically raised HER1 activity by impairing the ligand-induced ubiquitinylation and degradation of the activated receptor through destabilization of newly formed ubiquitin ligase Cbl complexes. This resistance can be overcome by more complete HER1 kinase inhibition. PTEN deficient cells are also extremely sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors and thus PARP inhibition is another hope for patients with PTEN deficiency.

LAPATINIB PLASMA LEVELS

Effective plasma concentrations of lapatinib might be assessed using the approaches similar to common therapeutic drug monitoring. Such testing has already been suggested in the case of another TKI, imatinib which has been studied in relation to plasma concentration impact on treatment response in patients treated with the compound for chronic myeloid leukemia (CML) and gastrointestinal stromal tumors. In the case of imatinib, higher plasma levels correlated with complete cytogenetic responses in CML patients. Plasma levels lower than those assessed as effective were significantly associated with worse treatment response. Imatinib plasma level evaluation supports the idea that a similar approach could be useful in lapatinib-treated patients. Lapatinib can be evaluated in patient blood samples. The recommended dose is not dependent on body weight. Lapatinib plasma level assessment could be a tool to identify patients in danger of treatment failure because of too low or too high lapatinib levels. Methods based on liquid chromatography and mass spectrometry have already been tested to determine lapatinib level in human plasma. Haouala et al. described a method useful for a wide range of currently used TKIs including lapatinib and they suggest that free plasma levels should be assessed to obtain accurate estimates of drug quantity available to affect tumor cells. Nevertheless, lapatinib plasma levels have not been published in association with therapy outcome. We applied a previously developed method for determination of imatinib in plasma for lapatinib, which is separated in 1.9 min under the same chromatographic conditions and we are currently evaluating the role of lapatinib plasma level assessment in therapy tailoring.

CONCLUSION

Lapatinib is a new therapeutic option for HER2+ BC patients. Interactions with other drugs metabolized by cytochromes P450 can influence lapatinib effectiveness, mainly with regard to CYP3A4 inhibitors and inducers. Resistance to lapatinib can be caused by genetic/epigenetic changes in tumor cells as well as by other factors leading to low and ineffective lapatinib concentrations in a tumor, e.g. reasons described in association with pharmacokinetics. At this time, only HER2 amplification/overexpression is used to select the best lapatinib therapy candidates in routine clinical settings. Further studies focusing on HER1 (EGFR) gene/protein status assessment promise to provide new data on its predictive role. PTEN loss and PIK3CA gene mutations are markers that could also predict treatment response. Secondary resistance appearing during lapatinib treatment caused by tumor cell changes in DNA or protein expression is difficult to assess in patients on lapatinib treatment. Repeated tumor samples are needed for such an examination and these are not usually available in clinical practice. Thus markers quickly and easily available for assessment may play an important role in therapy tailoring. Pharmacokinetic influence on lapatinib efficacy might be easily assessed by lapatinib plasma levels representing changes in drug metabolism. Lapatinib plasma level assessment may also be a tool for identifying patients at risk of treatment failure or toxicity because of too low or too high lapatinib levels. A prospective clinical study evaluating such an approach would provide evidence of lapatinib plasma level assessment and its application in routine clinical practice with the aim of optimizing and prolonging this efficient therapy.

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