

A review of lapatinib ditosylate in the treatment of refractory or advanced breast cancer

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Abstract: Breast cancer remains a leading cause of disease and death among women throughout the world. Despite advances in drug therapy, development of novel and improved drugs for breast cancer continues to be of great interest. Lapatinib is a novel dual receptor tyrosine kinase inhibitor that is a selective and potent inhibitor of ErbB-1 and ErbB-2 tyrosine kinases, both of which are growth promoting factors overexpressed in some breast cancers. Cell-based assays have proven lapatinib to be a potent inhibitor of ErbB-1 and ErbB-2 activation and breast cancer cell proliferation. In pharmacokinetic studies, lapatinib has shown mostly linear elimination kinetics over the daily dose range of 10–1600 mg and is metabolized by CYP3A4/5 and CYP2C19. Phase I, II, and III clinical trials involving lapatinib as monotherapy or in combination have shown promise for the treatment of advanced and metastatic breast cancer. Drug-drug interactions may occur secondary to concomitant administration of either CYP450 inhibitors or inducers. While lapatinib appear to be a promising addition to breast cancer therapy, several questions remain to be answered before its optimal role is elucidated.

Keywords: lapatinib, GW572016, breast cancer, tyrosine kinase inhibitor

Introduction

Breast cancer is the most common cause of cancer among women with over 1 million new cases estimated to occur worldwide each year (Cox et al 2006). Despite advances in treatment, breast cancer remains a leading cause of death in developed countries. For example, breast cancer is the second leading cause of cancer-related deaths in several countries, including the United States (Jemal et al 2006). In the United Kingdom, breast cancer is the most common cause of death in women aged 40–50 (McPherson et al 2000). Localized disease is associated with a substantially greater 5-year survival rate (greater than 95%) than metastatic disease (less than 25%) (Cox et al 2006). While strides have been made in both detection and treatment of breast cancer, the need for new and improved breast cancer therapy, including chemotherapeutic agents, clearly remains.

Pharmacologic therapy of breast cancer has been evolving and improving over the last half-century, and has increased in emphasis as the understanding of the natural history of breast cancer has shifted to being viewed as a disease that is systemic at the time of detection rather than localized and sometimes becoming systemic (Nabholtz and Gligorov 2005). In the 1970s, chemotherapy of breast cancer was characterized by non-anthracycline containing regimens, such as CMF (cyclophosphamide, methotrexate, 5-fluorouracil), and were more successful in the adjuvant setting rather than treatment of metastatic disease. Breast cancer chemotherapy was improved in the 1980s with the introduction of the anthracyclines, and led to the development of multiple doxorubicin and epirubicin-containing regimens with superior reductions in breast cancer recurrence and mortality as compared with CMF (Levine and Whelan 2006). Multiple novel chemotherapy agents were introduced in the 1990s for the

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treatment of breast cancer. Of these, the taxanes (paclitaxel, docetaxel) have emerged as particularly efficacious either as monotherapy or in combination with anthracyclines for treatment of metastatic breast cancer (Nabholtz and Gligorov 2005). The development and use of hormonal agents, such as tamoxifen, as adjuvant therapy has led to additional increases in the long-term survival rate for breast cancer (Early Breast Cancer Trialists' Collaborative 2005).

A recent major advance in the pharmacotherapy of breast cancer is the introduction of drugs with especially high selectivity for tumor-specific targets. Trastuzumab, approved in the late 1990s, is a monoclonal antibody drug that is highly selective for targeting ErbB-2 (human epidermal growth factor receptor-2, HER-2), which is overexpressed in some breast cancers (Slamon et al 1987; Slamon and Godolphin 1989). In a 2001 study, Slamon and colleagues found that patients receiving trastuzumab plus either doxorubicin/cyclophosphamide or single-agent paclitaxel for metastatic breast cancer therapy was associated with improved time-to-progression relative to patients who did not receive trastuzumab (Slamon et al 2001). Recently trastuzumab was shown to be of benefit when combined with paclitaxel after doxorubicin and cyclophosphamide in patients with surgically removed ErbB-2-positive breast cancer (Romond et al 2005).

Despite the aforementioned succession of improvements in breast cancer pharmacotherapy, the current extent of morbidity and mortality associated with the disease highlights the need for additional improvements in drug therapy. The development of targeted chemotherapy drugs holds the promise of retaining, and perhaps increasing, efficacy while minimizing traditional chemotherapy-related toxicity (Pegram et al 2005; Flaherty and Brose 2006). One such promising drug is lapatinib, an orally available receptor tyrosine kinase inhibitor that, like trastuzumab, is highly selective for tumor-specific targets found in some breast cancers (Moy and Goss 2006; Nelson and Dolder 2006).

Pharmacology

Receptor tyrosine kinases are transmembrane-bound enzymes important to cell signaling pathways that control cell differentiation and proliferation (Bennasroune et al 2004; Tibes et al 2005). Tyrosine kinases use adenosine triphosphate (ATP) to phosphorylate tyrosine residues on signaling proteins. Tyrosine kinase inhibitors are small molecule drugs that competitively inhibit tyrosine kinase activity by binding to the ATP binding site of tyrosine kinases (Lin and Winer 2004). Evidence has implicated the human epidermal growth factor

(HER) subfamily of receptor tyrosine kinases as important to the proliferation of some breast cancers; accordingly, the HER tyrosine kinases have become attractive targets for drug development (Slamon and Godolphin 1989; Hackel et al 1999). There are 4 members in the HER subfamily of receptor tyrosine kinases: (1) ErbB-1 (epidermal growth factor receptor, EGFR, HER-1), (2) ErbB-2 (human epidermal growth factor receptor-2, HER-2, neu), (3) ErbB-3 (human epidermal growth factor receptor-3, HER-3) and (4) ErbB-4 (human epidermal growth factor receptor-4, HER-4) (Hackel et al 1999; Lin and Winer 2004). Ligand binding to ErbB-1, ErbB-3 and ErbB-4 results in formation of homodimers and heterodimers among the 4 HER tyrosine kinases. ErbB-2 has no known ligands; however, it is the preferred heterodimerization partner for ErbB-1, ErbB-3 and ErbB-4 (Graus-Porta et al 1997). Ligand binding and dimerization of HER kinases results in tyrosine kinase activity leading to activation of downstream signaling pathways and subsequent tumor cell proliferation (El-Rayes and LoRusso 2004).

Research suggests that several members of the HER subfamily of tyrosine kinases are important to breast cancer pathogenesis and are therefore attractive therapeutic targets. Overexpression of ErbB-2, which is present in approximately 20–25% of breast cancer, is associated with aggressive disease and shortened disease-free survival and overall survival (Slamon et al 1987; Slamon and Godolphin 1989). ErbB-1 is of importance due to its association with ErbB-2, as evidence suggests that ErbB-1 and ErbB-2 work in synergy to produce an oncogenic effect (Graus-Porta et al 1997). Specifically, ErbB-2 dimerization with ErbB-1 increases the affinity for binding of epidermal growth factor (EGF) to ErbB-1 (Karunakaran et al 1996), and the binding of EGF to ErbB-1 subsequently increases the activation of ErbB-2 (King et al 1988). In addition to ErbB-2, ErbB-1 has also been found to be overexpressed in some breast cancers (Lin and Winer 2004).

Several types of clinically useful oncology drugs target the HER subfamily of tyrosine kinases including (1) monoclonal antibodies and (2) tyrosine kinase inhibitors. The monoclonal antibodies that target HER proteins are selective for a single target. For example, trastuzumab targets ErbB-2 (Nahta and Esteva 2003) and cetuximab targets ErbB-1 (Ng and Cunningham 2004). Most tyrosine kinase inhibitors currently approved for cancer treatment target a single tyrosine kinase signaling pathway. For example, erlotinib and gefitinib selectively target ErbB-1 (Langer 2004). A salient feature of lapatinib is its ability to simultaneously inhibit the tyrosine kinase activity of 2 members of the

HER subfamily of tyrosine kinases. Accordingly, lapatinib has been classified as a dual tyrosine kinase inhibitor and described as having a broader spectrum of signal inhibition activity (Xia et al 2002; Flaherty and Brose 2006). Specifically, lapatinib is a selective and potent inhibitor of ErbB-1 and ErbB-2 tyrosine kinases (Rusnak et al 2001a; Rusnak et al 2001b; Burris 2004). The dual inhibition ErbB-1 and ErbB-2, tyrosine kinases that appear to work in synergy for promoting breast cancer proliferation, has been suggested as an explanation for the more potent inhibition of cancer cell growth than is seen when targeting either ErbB-1 or ErbB-2 alone (Burris 2004).

Multiple *in vitro* studies have examined the activity of lapatinib for inhibition of ErbB-1 and ErbB-2 activity and inhibition of breast cancer cell proliferation in a variety of conditions. Lapatinib appears to be a potent inhibitor of ErbB-1 and ErbB-2, as evidenced by cell-free biochemical kinase activity assays in which the 50% inhibitory concentration (IC₅₀) of lapatinib for ErbB-1 and ErbB-2 was 10.8 and 9.2 nM, respectively (Rusnak et al 2001b). In cell-based assays the potency of lapatinib for inhibition of ErbB-2-overexpressing breast cancer cell growth varies depending on the cell line. For example, lapatinib is a relatively potent inhibitor of BT474 breast cancer cell growth (IC₅₀ 100 nM) but is 30- to 40-fold less potent against MCF-7 and T47D breast cancer cells (Rusnak et al 2001b). Additional cell-based studies have shown that lapatinib inhibits ErbB-1 and ErbB-2 activation and cell proliferation in breast cancer cell lines that overexpress either ErbB-1 or ErbB-2 (Xia et al 2004; Zhou et al 2004; Spector et al 2005). Several cell-based studies have demonstrated that lapatinib combined with trastuzumab enhances breast cancer cell apoptosis in ErbB-2-overexpressing breast cancer cells and breast cancer cells resistant to trastuzumab monotherapy (Xia et al 2005; Konecny et al 2006). Finally, recent evidence suggests that lapatinib, unlike trastuzumab and gefitinib, induces down-regulation of the apoptosis inhibitor survivin, which in turn leads to apoptosis of breast cancer cells (Xia et al 2006).

Pharmacokinetics

Lapatinib is administered as an oral drug formulated as the monohydrated ditosylate derivative. In initial pharmacokinetic and safety studies, the daily dosage range of lapatinib was 10–1600 mg (Bence et al 2005; Burris et al 2005). Larger phase II and phase III trials have typically used a dosing range of 750–1500 mg (Table 2). Lapatinib has generally displayed linear elimination pharmacokinetics over a wide daily dosage range (10–1600 mg/day).

Table 1 Lapatinib in brief

Mechanism of action	Receptor tyrosine kinase inhibitor at ErbB-1 and ErbB-2
Route of administration	Oral as lapatinib ditosylate
Daily dose range	750–1500 mg given once or twice daily
Metabolism	CYP3A4/5 and CYP2C19
Common adverse effects	Rash, diarrhea, nausea, fatigue, anorexia
Drug-drug interactions	CYP450 inhibitors may increase AUC of lapatinib CYP450 inducers may decrease AUC of lapatinib

At the time of writing, oral bioavailability data had not been published for lapatinib; however, one study suggests that the oral absorption of lapatinib is partially limited by low solubility and that recent food intake may contribute to variability in absorption (Burris et al 2005). Following an oral dose, onset of absorption is delayed about 30 minutes and peak serum concentrations (C_{max}) occur after 3–4 hours (Bence et al 2005). In the dosage range of 10 to 250 mg, the peak serum concentrations of lapatinib increased in a dose-proportional manner.

With chronic oral therapy lapatinib accumulates in the body (Bence et al 2005). Accordingly, single-dose pharmacokinetic studies do not reflect the area under the curve (AUC) and elimination half-life of lapatinib that would result from a chronic oral administration dosing regimen used for breast cancer therapy. At doses over 100 mg per day, lapatinib trough levels increase by approximately 50% over 6 to 8 days of therapy. This finding has led investigators to conclude that lapatinib has an effective elimination half-life of approximately 24 hours with chronic dosing, as opposed to the measured elimination half-life of 6 to 11 hours observed with single-dose studies, suggesting that the preferred dosing interval is once daily (Bence et al 2005).

Lapatinib undergoes both hepatic and intestinal metabolism by cytochrome P450 isoenzymes (CYP450). *In vitro* studies indicate that lapatinib undergoes oxidative metabolism predominantly by the CYP3A4/5 isoforms and to a lesser degree by the CYP2C19 isoform (Herendeen et al 2004; Smith et al 2004). Neither the percent of the dose that is eliminated by metabolism nor the major route(s) of elimination for lapatinib have been published at the time of writing.

Efficacy

Lapatinib's efficacy in breast cancer has been examined in several trials and is summarized in Table 2. Most of these investigations were ongoing open-label, Phase I

Table 2 Clinical trials involving lapatinib in patients with breast cancer

Author	Study phase	Sample size	Cancer	Lapatinib's place in therapy	Lapatinib regimen	Efficacy outcomes (% of study population)
Stornio et al 2005	I	27	Metastatic breast cancer	2nd-line treatment used in combination regimen	750–1500 mg daily plus trastuzumab	Patients receiving lapatinib were noted to have achieved: 6 complete or partial responses (22%), and 10 disease stabilizations (37%) Time to progression and overall survival not reported
Blackwell et al 2005	II	81	Metastatic breast cancer	2nd-line treatment used as monotherapy	Not reported	Patients receiving lapatinib were noted to have achieved: 7 complete or partial responses (9%) and 12 disease stabilizations (15%) Time to progression and overall survival not reported
Gomez et al 2005	II	13	Advanced or metastatic breast cancer	1st-line treatment used as monotherapy	1500 mg daily or 500 mg twice daily	Patients receiving lapatinib were noted to have achieved: 5 partial responses (39%) and 6 disease stabilizations (46%) Time to progression and overall survival not reported
Spector et al 2006	II	17	Relapsed or refractory inflammatory breast cancer	2nd-line treatment used as monotherapy	1500 mg daily	Patients receiving lapatinib were noted to have achieved: 8 complete or partial responses (47%) Time to progression and overall survival not reported
Geyer et al 2006	III	321	Refractory advanced metastatic breast cancer	2nd-line treatment used in combination regimen	1250 mg daily plus capecitabine 2000 mg/m ² on days 1–14 of 3-week cycle (vs. capecitabine monotherapy)	All responders were overexpressors of Erb2 (11 of the 17 patients) Patients receiving lapatinib were noted to have achieved: 23 complete or partial responses (15%) Median time to progression significantly favored patients treated with lapatinib and capecitabine (37 weeks) compared to patients treated with only capecitabine (20 weeks)

**Table includes studies that focused on breast cancer.

and II trials with small numbers of patients. Nonetheless, these studies demonstrate substantial promise for lapatinib. Results of three Phase I or II studies (Blackwell et al 2005; Gomez et al 2005; Storniolo et al 2005) have been published involving lapatinib's use in advanced or metastatic breast cancer. These studies involved 121 patients receiving oral doses of lapatinib between 750 and 1500 mg per day. Response rates in these three trials ranged from 9% to 39% and stabilization of disease for patients treated with lapatinib were noted to be between 15% and 46% among the three trials. The response rates reported in these trials are relatively low; however, findings from these studies must be examined in the context of metastatic, refractory and/or relapsed breast cancer (ie, generally low response rate and poor prognosis). The ability of lapatinib to effect positive results in a subset of patients with traditionally difficult to treat cancer is also highlighted by results from Spector and colleagues (Spector et al 2006) in a trial involving inflammatory breast cancer. Inflammatory breast cancer is relatively uncommon but is aggressive and possesses a poor prognosis (Ueno et al 1997; Peck 2006). In this study involving 17 individuals with relapsed or refractory inflammatory breast cancer, a complete or partial response rate of 47% was reported. This number rose to 82% when examining just the cohort that overexpressed ErbB2.

The most encouraging results involving lapatinib are from a Phase III trial involving more than 300 patients with refractory advanced metastatic breast cancer randomized to either lapatinib and capecitabine or capecitabine monotherapy. Patients in the combination group received 1250 mg daily of lapatinib and 2000 mg/m² of capecitabine on days 1–14. Patients enrolled into the capecitabine monotherapy group received 2500 mg/m² also administered on days 1–14. Both treatment arms received medications in three week cycles. Ninety-six percent of patients had stage IV breast cancer and 80% of patients had at least two metastatic sites. Ninety-eight percent of patients had previously received anthracyclines, taxanes, and trastuzumab. Thus, these patients had significant disease that had progressed or relapsed despite a variety of standard chemotherapy agents. The investigators noted substantial benefits favoring patients receiving the combination of lapatinib and capecitabine compared to capecitabine alone, including median time to progression (36.9 weeks vs. 19.7 weeks, $p < 0.001$), patients who progressed or died (28% vs. 43%, $p < 0.001$) and overall survival (22.5% vs. 14.3%, $p = 0.113$) (Geyer et al 2006). Beneficial results of the study led to the trial's independent data monitoring

committee recommending premature study discontinuation (GlaxoSmithKline 2006).

A substantial proportion of women with metastatic breast cancer will experience central nervous system (CNS) disease. Lin and colleagues (Lin et al 2006) examined the efficacy and safety of lapatinib in 39 such patients. The mean age of patients was 52 years and 44 percent of these women were ErbB-2 positive. All patients had developed CNS lesions while on trastuzumab and most had progressed despite radiation. In addition, 90% of patients had received previous taxanes and 67% had received anthracyclines. Eligible individuals received 750 mg of lapatinib twice daily in an open-label fashion for 8 weeks. Imaging was performed at baseline, week 1, and week 8 to determine the objective response rate in the brain. In terms of efficacy, two patients achieved a partial response rate based on Response Evaluation Criteria In Solid Tumors (RECIST) and five additional subjects were found to have experienced at least a 30% volumetric reduction in their CNS lesions. The median time to treatment failure was approximately 3 months. In terms of safety data, the most common grade 3 toxicities were diarrhea (21%), fatigue (16%), and rash (5%). No patients developed grade 4 toxicities. Furthermore, no grade 3 or 4 declines in left ventricular ejection fraction were noted; however, 4 cases of asymptomatic reductions in ejection fraction were reported (Lin et al 2006; Peck 2006). The study by Lin and colleagues found only low objective response rates of lapatinib as adjuvant therapy in patients with metastatic cancer involving the brain. Nonetheless, some activity was demonstrated. Such a finding may prove to be important when considering the poor prognosis of patients with metastases to the brain (Engel et al 2003).

Although not all predictors of lapatinib response are currently understood, selecting patients who are more likely to respond to the dual tyrosine kinase inhibitor appears important. For example, in an analysis of the biological effect of lapatinib on tumor tissue (Burris et al 2005), investigators reported that patients with breast cancer who had higher pretreatment expression of ErbB-2 and activated ErbB-2 (p-ErbB2) were more likely to achieve a complete or partial response. This finding is supported by Spector and colleagues' (Spector et al 2006) examination of lapatinib monotherapy in relapsed or refractory inflammatory breast cancer. In this study, 11 patients were overexpressors of ErbB-2 and six were not. Eight of the 11 overexpressors achieved at least a partial response, while none of the ErbB-2 non-overexpressors responded to lapatinib.

Although most published trials of lapatinib involve its use in breast cancer, results of several investigations have been published regarding other solid tumors. Relatively limited activity has been reported with lapatinib as second-line therapy in metastatic colorectal cancer (Fields et al 2005) and in bladder cancer (Wulfing et al 2005). Ongoing trials are also examining lapatinib's efficacy in lung and renal cell cancer (Johnston and Leary 2006).

Ongoing breast cancer trials (Johnston and Leary 2006)

There are a number of ongoing phase II and III trials with lapatinib in breast cancer. These investigations involve lapatinib in both treatment refractory patients and in patients where lapatinib represents first-line therapy. Once completed, these studies should provide valuable information regarding the best uses of lapatinib in breast cancer. The primary endpoints of these investigations are generally time to disease progression for the phase III trials and objective response rate for the phase II trials. Subjects per study range from 60 to 1200. In patients with ErbB-2-positive refractory breast cancer, lapatinib is being examined in an open-label fashion as monotherapy (EGF105084, EGF103009) and in randomized controlled trials with and without trastuzumab (EGF104900) or fulvestrant (CALGB 40302). Ongoing investigations of lapatinib as first-line therapy involve various combinations of lapatinib with taxanes utilizing a number of study designs. Three phase III, randomized, double-blind, controlled trials (EGF104383, EGF104535, and EGF3001) involve patients with no previous treatment for metastatic breast cancer being randomized to active treatments of paclitaxel and lapatinib with or without trastuzumab. These trials will help to provide information on whether the addition of lapatinib will increase the efficacy of current taxane/trastuzumab-based regimens. An additional phase III, randomized, double-blind, placebo-controlled trial (EGF 30008) is examining the effects of letrozole with or without lapatinib in postmenopausal women with metastatic breast cancer. This particular investigation is treating patients without regard to ErbB-2 status. Such a study has the potential to provide valuable data regarding the place of lapatinib in treatment sequences involving hormonal therapies such as tamoxifen (Johnston and Leary 2006).

Adverse effects

Safety data derived from phase I, II, and III trials involving lapatinib have demonstrated the medication's relatively tolerable side effect profile. In the largest phase III study published

to date (Geyer et al 2006), the prevalence of side effects leading to discontinuation were similar between patients receiving lapatinib and capecitabine (14%) and those patients receiving only capecitabine (11%) (GlaxoSmithKline 2006). The most common side effects reported in patients receiving both lapatinib and capecitabine were diarrhea, hand-foot syndrome, and rash. The vast majority of these toxicities were grade 3 or less. Grade 3 diarrhea was reported in 12% of the lapatinib and capecitabine group and 11% of the capecitabine monotherapy group. Grade 3 palmar-plantar erythema occurred in 6% of lapatinib and capecitabine-treated patients and 5% of the capecitabine-treated patients. Rash was found in 3% of the lapatinib group and 7% in the capecitabine monotherapy group. Four patients in the lapatinib group were noted to have experienced a cardiac side effect (ie, reduction in left ventricular ejection fraction), all of which were asymptomatic (Peck 2006).

The adverse effect profile of lapatinib, when derived from phase I and II trials, is similar to that of the above-mentioned phase III trial. For instance, in a phase I trial involving a variety of carcinomas (Burriss et al 2005), the most common side effects associated with doses of lapatinib ranging from 500–1600 mg per day were diarrhea (42%), rash (31%), nausea (13%), and fatigue (10%). Ninety six percent of these reported adverse effects were deemed mild or moderate. In another Phase I investigation involving doses of lapatinib up to 1800 mg daily, the most frequently reported side effects were also rash, diarrhea, nausea, fatigue, and anorexia. All of these were considered mild to moderate in severity (Versola et al 2004). Very similar side effects have been reported in Phase II trials. Overall, grade 4 (life-threatening or disabling adverse event) or 5 (death related to adverse event) have been rarely reported in clinical trials involving lapatinib.

Reports of decreased cardiac function have surfaced from individual trials of lapatinib. Perez and colleagues (Perez et al 2006) pooled safety data from 2,812 subjects who had received lapatinib in clinical trials. Cardiac risk factors including age, presence of existing cardiovascular disease, exposure to mediastinal radiation therapy, and treatment with chemotherapeutic agents with known cardiac effects were collected. The primary safety outcome was a significant change in left ventricular ejection fraction (LVEF) (grade 3 toxicity or at least a 20 percent decline in LVEF). Only 37 of the 2,812 patients (1.3%) who had received lapatinib were reported to have experienced decreased LVEF. The median age of these 37 individuals was 59 years and 68 percent were female. Twenty-two of the patients were receiving lapatinib monotherapy and 15 were receiving additional

chemotherapeutic agents. In the majority of cases, decreased LVEF was noted within nine weeks of lapatinib initiation. The majority of patients were asymptomatic and most symptomatic patients responded to standard heart failure treatments in a timely manner. Thirty-four of the 37 individuals who experienced declines in LVEF had confounding factors that may have contributed to their reduced LVEF, making the determination of a clear relationship between lapatinib use and depressed cardiac function difficult. Nonetheless, the decrease in LVEF that was experienced by these persons was noted to have resolved or improved in 57% of cases, 50% of which occurred with continued lapatinib treatment. Thus, results from Perez and colleagues support the notion that lapatinib-associated declines in LVEF, although potentially serious, are uncommon, usually asymptomatic, and generally reversible (Peck 2006; Ruiz-Palacios et al 2006).

Drug interactions

At this time there is little published data regarding the drug-drug interaction potential of lapatinib. In general, lapatinib appears to have little potential to alter the pharmacodynamic effects of other medications. Evidence from a phase I pharmacokinetic study in which lapatinib and paclitaxel were administered either alone or in combination to 18 cancer patients suggested that treatment-related toxicities such as neuropathy, diarrhea, rash and myalgias occurred in greater intensity with the combination therapy (Jones et al 2004).

Given the fact that lapatinib is metabolized by CYP3A4, CYP3A5 and CYP2C19, a likely source of drug-drug interactions would be concomitant use with other drugs that inhibit or induce the activity of these CYP450 isoforms. Of the CYP450 isoenzymes, CYP3A4 is especially important in terms of drug-drug interactions due to the fact that it is the most plentiful CYP450 in the liver and accounts for more drug metabolism than any other CYP450 (Wilkinson 2005; Zhou et al 2005).

The effect of CYP3A4 inhibition on the pharmacokinetics of a single 100 mg dose of lapatinib was studied in an open-label, randomized, two-way crossover study of 22 healthy adults using 200 mg twice daily of ketoconazole, a potent inhibitor of CYP3A4 (Smith et al 2004). In this study ketoconazole administration resulted in a 3.6-fold increase in lapatinib AUC and an approximately 2-fold increase in maximum blood concentration (C_{max}) and elimination half-life, suggesting that concomitant use of CYP3A4 inhibitors with lapatinib may cause clinically important drug-drug interactions. In a study with similar methodology, the effect of carbamazepine, a known inducer of CYP450 metabolism,

on the pharmacokinetics of a single lapatinib dose was studied (Herendeen et al 2004). Results from this study showed that carbamazepine administration resulted in 72% and 58% decreases in lapatinib AUC and C_{max} , respectively. Interestingly, the elimination half-life of lapatinib was unchanged in this study. Both of these studies only examined the effect of CYP450 inhibition and induction on pharmacokinetic parameters for a single dose of lapatinib. Certain pharmacokinetic parameters, such as the elimination half-life, change as lapatinib accumulates in the body with multiple-dosing (Bence et al 2005), and results of studies utilizing only a single dose of lapatinib may not accurately extrapolate to the expected lapatinib clinical scenario in which patients receive chronic therapy. Regardless, both studies highlight the fact that clinicians should be vigilant for potential drug-drug interactions if lapatinib is used with other medications that either induce or inhibit CYP450 activity.

Lapatinib's future

Lapatinib is an oral dual receptor tyrosine kinase inhibitor that offers a wider spectrum of signal transduction inhibition and has demonstrated substantial promise for breast cancer treatment in Phase I, II, and III trials. A number of unresolved issues regarding lapatinib exist, some of which will hopefully begin to be resolved with results of pending investigations. One of the therapeutic challenges associated with the use of lapatinib is its role in breast cancer treatment. Specifically, should this medication be used in conjunction with or in place of trastuzumab? In what sequence with such agents as tamoxifen and anastrozole will lapatinib produce the most efficacy? Does lapatinib have a role as first-line therapy in breast cancer as monotherapy or in conjunction with other chemotherapeutic agents? If lapatinib is proven to improve survival in the adjuvant setting in future trials, then how long do patients need to continue therapy? Another challenge is to determine how a patient's ErbB-1 and ErbB-2 status affects response rates and safety of lapatinib. Additional data regarding pharmacokinetics and the drug-drug interaction potential in the target population of lapatinib will be necessary to ensure optimal and safe use of lapatinib. Yet another area of need is to determine lapatinib's role in other types of cancer.

Lapatinib is representative of emerging novel anticancer drugs that are targeted to tumor-specific markers and offer the promise of improved efficacy and decreased toxicity relative to traditional cancer chemotherapeutics. The potential for lapatinib to improve some aspects of breast cancer therapy appears to be substantial. However, multiple questions

remain to be answered before the optimal clinical role of lapatinib emerges.

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