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Lapatinib

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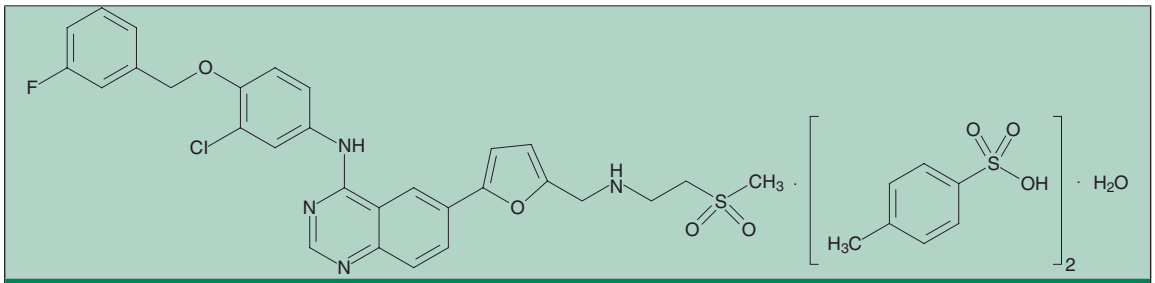
Contents

Abstract

- Lapatinib inhibits tyrosine phosphorylation of both epidermal growth factor receptor and human epidermal receptor (HER) 2, thus preventing receptor activation.
- Preliminary evidence suggests that clinical response to lapatinib may be linked to the extent of baseline HER2 gene expression.
- In a randomised, open-label, phase III trial, the median time to progression was significantly longer with lapatinib in combination with capecitabine than with capecitabine monotherapy (6.2 vs 4.3 months) in patients with locally advanced or metastatic HER2-positive breast cancer who were refractory to previous therapy.
- The overall response rate was also significantly higher in patients receiving lapatinib plus capecitabine than in those receiving capecitabine alone.
- Most adverse events in this trial were mild to moderate in severity and of a similar nature to those seen with capecitabine monotherapy.

Features and properties of lapatinib (Tykerb®)	
Indication	
Locally advanced or metastatic, human epidermal receptor (HER) 2-positive breast cancer refractory to prior therapy including an anthracycline, a taxane and trastuzumab; to be used in combination with oral capecitabine	
Mechanism of action	
A dual tyrosine kinase inhibitor that reversibly inhibits the tyrosine kinase activity of both epidermal growth factor receptor and HER2	
Dosage and administration	
Dosage	1250mg once daily on days 1–21 in combination with oral capecitabine 2000 mg/m^2/day on days 1–14 of a 21-day cycle
Route of administration	Oral
Pharmacokinetic profile (after 1250 mg/day for 6–7 days [steady state])	
Geometric mean peak plasma concentration	2.43 mg/L
Geometric mean area under the plasma concentration-time curve	36.2 mg • h/L
Terminal elimination half-life after a single dose	14.2h
Most frequent adverse events of any severity (incidence ≥20% in any treatment group)	
Diarrhoea, palmar-plantar erythrodysaesthesia, nausea, rash, vomiting, fatigue	



Lapatinib ditosylate

Breast cancer is the most common cancer worldwide, with ≥1.1 million new cases diagnosed annually, accounting for 23% of all cancers diagnosed in women.[1] Human epidermal receptor (HER) 2 is a type 1 receptor tyrosine kinase belonging to a family of receptor proteins, including epidermal growth factor receptor (EGFR/HER1), HER2, HER3 and HER4, which is overexpressed in 25–30% of breast cancer patients, and is associated with a high rate of cancer recurrence and poor prognosis for patients.[2-4]

The use of trastuzumab, a human anti-HER2 monoclonal antibody, as a single agent[5] or in combination with chemotherapy,[5,6] is recommended in HER2-positive breast cancer patients. However, trastuzumab therapy is administered intravenously, is associated with acquired resistance and, because it cannot penetrate the blood-brain barrier, is also associated with an increased incidence of brain metastases in breast cancer patients.[2,3] In order to overcome these limitations, small, orally administered molecules, such as lapatinib (Tykerb®)[1], erlotinib and gefitinib, which target the HER family of receptors, have been developed.

Lapatinib is an oral dual tyrosine kinase inhibitor that binds to the tyrosine kinase domain of both EGFR and HER2 receptors. The US National Comprehensive Cancer Network treatment guidelines recommend lapatinib plus capecitabine therapy as an option in patients with locally advanced or metastatic HER2-positive breast cancer refractory to prior therapy including an anthracycline, a taxane and trastuzumab.[5] This review focuses on the use of oral lapatinib (in combination with oral capecitabine) in patients with locally advanced or metastatic HER2-positive breast cancer refractory to previous therapy.

1. Pharmacodynamic Profile

This section provides an overview of the pharmacodynamic properties of lapatinib, with the focus being on data relevant to breast cancer.

In Vitro/Animal Studies

- Lapatinib, a 4-anilinoquinazoline kinase inhibitor, reversibly inhibits the tyrosine kinase activity of both EGFR and HER2; the estimated dissociation constant values were 3 and 13 nmol/L, respectively.[7,8] By contrast, trastuzumab inhibits only HER2-mediated signalling.[2]
- Lapatinib has a slow rate of dissociation from the tyrosine kinase receptor domain (half-life ≥300 minutes),[7] which may result in prolonged inhibition of tyrosine kinase activity in tumour cells.[8] It competes for the adenosine triphosphate (ATP) binding site on the tyrosine kinase domains of both EGFR and HER2, thus preventing the use of ATP as a cofactor for phosphorylation of the tyrosine residue, an important step during receptor activation.[4,9] The slow dissociation of lapatinib from EGFR is thought to be associated with changes in the conformation of the bound molecule.[8]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

- Tyrosine phosphorylation is potently inhibited by lapatinib.[10] *In vitro* treatment with 10.2 and 9.8 nmol/L of lapatinib resulted in 50% inhibition (IC_{50}) of tyrosine phosphorylation of EGFR and HER2 in biochemical assays.[10] Lapatinib also inhibited insulin-like growth factor (IGF)-1-mediated signalling *in vitro*; IGF-1 receptor signalling has been implicated in acquired resistance to trastuzumab therapy.[11]
- In contrast to trastuzumab and gefitinib (which had little effect on either parameter), lapatinib inhibited survivin protein expression and subsequently increased tumour cell apoptosis in a concentration-dependent manner in an HER2-overexpressing breast cancer cell line *in vitro*; overexpression of survivin may protect breast cancer cells from apoptotic stimuli.[12] Clinical response in a small biomarker study also correlated with inhibition of survivin expression in tumour biopsies.[13]
- Following 18 days of therapy, intraperitoneal lapatinib significantly reduced tumour volume of mouse xenografts expressing a truncated HER2 receptor relative to saline treatment; trastuzumab had no effect on tumour volume.[14] This effect may have clinical potential; response to trastuzumab appears to be higher in patients expressing full length HER2 than in those with the truncated form.[14]
- Lapatinib interacts synergistically with trastuzumab *in vitro*.[15,16] Furthermore, unlike that of trastuzumab, the antitumour effect of lapatinib in HER2-overexpressing breast cancer cell lines appears to be independent of the presence of the tumour suppressor phosphatase and tensin homologue deleted on chromosome 10 (PTEN), a phosphatase that is frequently (50% of breast cancers) lost in tumours, for example, through mutation.[17]
- In mice, oral lapatinib plus tamoxifen for 35 days significantly ($p < 0.01$) reduced tumour volume relative to tamoxifen alone in tamoxifen-resistant breast cancer xenografts.[18]

Clinical Studies

The effects of lapatinib on the expression of HER2 and EGFR biomarkers were assessed in 14 heavily pretreated women with metastatic breast cancer (12 were HER2-positive, 11 were EGFR-positive and 11 had received trastuzumab previously).[13] Patients received oral lapatinib 500–1600mg once daily before immunohistochemical staining of biopsies on day 21. Preliminary biomarker data are also available from the large randomised trial of lapatinib plus capecitabine in women with advanced, refractory, HER2-positive breast cancer (outlined in section 3).[19]

- Immunohistochemical staining of tumour biopsies showed that, relative to baseline, phosphorylation of biomarkers (e.g. EGFR and HER2) was inhibited and apoptosis of tumour cells was enhanced in patients responding to lapatinib therapy (four patients had partial response).[13]
- Clinical response to lapatinib therapy correlated with higher baseline levels of several biomarkers, including HER2 and IGF-1 receptors.[13] Similarly, preliminary data from the large phase III trial (section 3) indicate that response and clinical benefit rates (but not time to progression) increase with increased HER2 gene expression.[19]
- The small size of lapatinib (580 kDa) allows it to penetrate the blood-brain barrier to treat brain metastases.[20] In contrast, trastuzumab (148 000 kDa) does not penetrate the blood-brain barrier.[21]

2. Pharmacokinetic Profile

This section provides an overview of the pharmacokinetic properties of lapatinib, which have been evaluated in healthy volunteers[22] and in heavily pretreated patients with EGFR and/or HER2-overexpressing metastatic cancers.[23] Data are also available from the manufacturer's US prescribing information (recipient type not specified).[7]

- The absorption of oral lapatinib is incomplete and variable; the drug is detected in the serum after a median of 0.25 hours (range of 0–1.5 hours).[7] Low solubility of lapatinib and first-pass metabolism by the cytochrome P450 (CYP) isoenzymes 3A4 and 3A5 may restrict absorption of the drug resulting in variable systemic exposure.[23] In cancer patients receiving lapatinib 175–1800mg once daily for 14 days, peak plasma concentrations (C_{max}) were reached ≈4 hours after administering the dose.[24] In

healthy volunteers receiving lapatinib 100 or 175mg once daily, steady-state plasma concentrations were reached within 6–7 days.[22]

- After lapatinib 1250mg once daily, the steady-state (6–7 days) geometric mean C_{max} and the geometric mean area under the plasma concentration-time curve (AUC) values were 2.43 mg/L and 36.2 mg • h/L.[7] The steady-state AUC of lapatinib was ≈2-fold higher when the same daily dose was administered as divided doses.[7] In cancer patients receiving once-daily lapatinib 500–1600mg, an ≈2-fold accumulation of the drug was observed on day 20 relative to day 1.[23]
- Systemic exposure to the drug is increased (AUC ≈3- and ≈4-fold higher) when lapatinib is administered with low- or high-fat meals.[7]
- More than 99% of lapatinib is bound to albumin and alpha-1 acid glycoprotein. Lapatinib is extensively metabolised to several oxidated metabolites largely by the CYP isoenzymes 3A4 and 3A5, and to a small extent by CYP2C19 and CYP2C8, each metabolite accounting for ≤14% of the dose recovered in the faeces or ≤10% of the drug concentration in the plasma.[7]
- Elimination of lapatinib is primarily through metabolism, with 27% (median value) of the oral dose recovered unchanged from the faeces and <2% excreted via the kidneys.[7] The terminal elimination half-life of lapatinib after a single dose is 14.2 hours, but accumulation results in an effective half-life of 24 hours.[7]
- Following a single oral dose of lapatinib 100mg, 14% and 63% increases in systemic exposures were observed in patients with moderate (Child-Pugh class B; n = 8) or severe (Child-Pugh class C; n = 4) hepatic impairment over those with normal hepatic function (n = 8). Caution is advised and a dosage reduction should be considered in patients with severe hepatic impairment.[7] No studies have evaluated the effect of renal impairment, age, gender or race on the pharmacokinetics of lapatinib.[7]

Drug Interactions

- Concurrent administration of lapatinib and capecitabine does not significantly alter the pharmacokinetics of either drug.[7]
- However, as lapatinib is metabolised extensively by CYP3A4, strong inhibitors (e.g. ketoconazole, itraconazole, clarithromycin and atazanavir) or inducers (e.g. carbamazepine, dexamethasone, phenytoin and rifampicin) of the isoenzyme may alter the pharmacokinetics of the drug.[7] A dosage reduction is recommended in patients receiving lapatinib concomitantly with strong inhibitors of CYP3A4 and the dosage should be titrated up to 4500 mg/day in patients receiving lapatinib concomitantly with inducers of CYP3A4.[7]
- A dosage reduction is also recommended for concomitantly administered medications that have narrow therapeutic windows and are substrates of CYP3A4 or CYP2C8; both isoenzymes are inhibited by lapatinib *in vitro*.[7]
- Lapatinib appears to be a substrate for the efflux transporters breast cancer resistance protein and P-glycoprotein (P-gp). Furthermore, at clinically relevant concentrations, it may inhibit these efflux transporters and the hepatic uptake transporter OATP 1B1.[7] Thus, caution is advised when lapatinib is administered concomitantly with drugs that inhibit, or are substrates of, P-gp.[7]

3. Therapeutic Efficacy

The efficacy of lapatinib administered concomitantly with capecitabine versus capecitabine alone was evaluated in women (n = 399; aged 26–83 years) with locally advanced or metastatic, refractory, HER2-positive breast cancer in a randomised, open-label, multicentre, phase III trial.[7,19,25] Patients received oral lapatinib 1250mg once daily on days 1–21 plus oral capecitabine 2000 mg/m^2/day on days 1–14 of a 21-day cycle, or oral capecitabine 2500 mg/m^2/day on days 1–14 of a 21 day cycle; lapatinib was administered 1 hour before or after breakfast and capecitabine was administered as two divided doses.[7,19]

In a prespecified interim analysis (n = 324) by an independent committee, lapatinib plus capecitabine combination therapy was demonstrated to be superior to capecitabine monotherapy in terms of the primary endpoint of time to progression of disease.[25] As a result, further enrolment of patients was discontinued, and patients receiving capecitabine alone were given the option of initiating lapatinib therapy.[25] This section will focus on the final analysis of data accumulated up to that point, which is available from the US prescribing information[7] and a poster plus oral presentation.[19]

Women enrolled in the trial had locally advanced (T4 primary tumour and stage IIIB or IIIC disease) or metastatic HER2-positive breast cancer that had progressed despite therapy including an anthracycline, a taxane and trastuzumab.[19,25] Previous therapy included at least four cycles of anthracycline and taxane-based regimens administered concurrently or separately, or two cycles of the regimen if disease progressed during therapy; trastuzumab had been administered alone or in combination with chemotherapy for at least 6 weeks.[25] HER2 positivity was defined as immunohistochemical staining for HER2 of grade 3+ intensity, or of grade 2+ intensity confirmed by fluorescence *in situ* hybridisation.[19,25]

Patients had a life expectancy of ≥12 weeks, an Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease according to modified Response Evaluation Criteria in Solid Tumours (RECIST) and left ventricular ejection fraction (LVEF) within the normal range for the institution where the patient was enrolled.[19,25] Women who had received prior capecitabine therapy were excluded from the study; prior treatment with fluorouracil was permitted.[19]

The primary endpoint was the time to progression of disease (from randomisation to disease progression or death due to breast cancer).[7,19,25] Secondary endpoints included overall survival, overall response rate (complete or partial response) and the rate of clinical benefit (complete response, partial response or stable disease for 6 months);[19,25] response was evaluated using modified RECIST criteria.[25] Patients were evaluated every 6 weeks for the first 6 months and every 12 weeks thereafter.[25] Analyses were based on the intent-to-treat (ITT) population.[7,19,25]

- The time to progression of disease was significantly longer in patients receiving lapatinib plus capecitabine (n = 198) than in those receiving capecitabine alone (n = 201) in the final analysis of data from the pivotal trial (median 6.2 vs 4.3 months; p = 0.00013; hazard ratio [HR] 0.57 [95% CI 0.43, 0.77]; figure 1).[7,19] Similarly, in the interim analysis, the time to progression of disease was significantly extended in lapatinib plus capecitabine (n = 163) relative to capecitabine monotherapy (n = 161) recipients (median 8.4 vs 4.4 months; p < 0.001; HR 0.49 [95% CI 0.34, 0.71]).

- In the final analysis, the overall response rate was also significantly higher in patients receiving lapatinib plus capecitabine combination therapy than in those receiving capecitabine alone (24% vs 14%; p = 0.017; odds ratio 1.9 [95% CI 1.1, 3.4]).[7,19] Median overall survival was similar in the two treatment groups (15.6 vs 15.3 months); partial response rates were 23% versus 14% in lapatinib plus capecit-

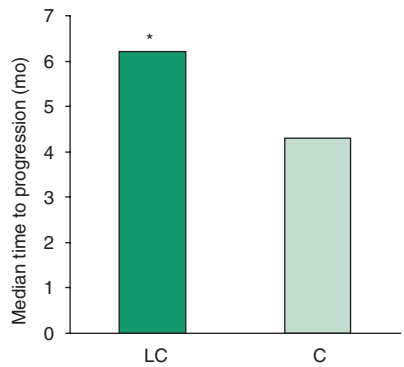


Fig. 1. Efficacy of lapatinib plus capecitabine therapy in patients with locally advanced or metastatic, refractory, human epidermal receptor type 2-positive breast cancer. The median time to disease progression in the intent-to-treat population of patients receiving oral lapatinib 1250mg once daily on days 1–21 plus oral capecitabine 2000 mg/m^2/day (as two divided doses) on days 1–14 (n =198) of a 21-day cycle (LC), or oral capecitabine 2500 mg/m^2/day (as two divided doses) on days 1–14 (n = 201) of a 21-day cycle (C) in a randomised, open-label, multicentre, phase III trial.[7] * p = 0.00013.

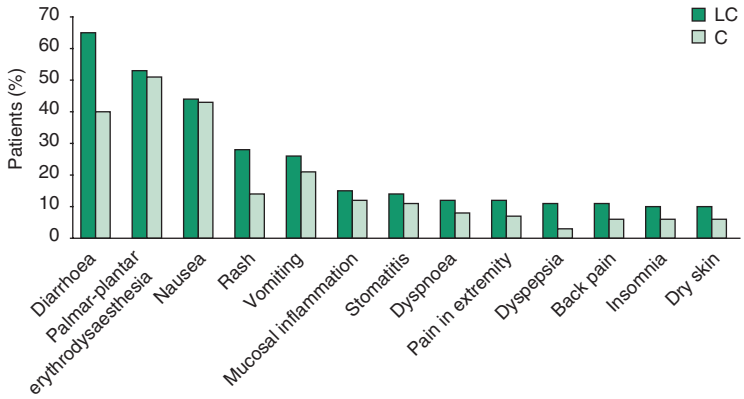


Fig. 2. Tolerability of lapatinib plus capecitabine in patients with locally advanced or metastatic, refractory, HER2-positive breast cancer. The most frequent (i.e. incidence ≥10% in any treatment group) all-grade adverse events occurring in more combination therapy than monotherapy capecitabine recipients are presented. Intent-to-treat patients received oral lapatinib 1250mg once daily on days 1–21 plus oral capecitabine 2000 mg/m^2/day (as two divided doses) on days 1–14 (n =198) of a 21-day cycle (LC), or oral capecitabine 2500 mg/m^2/day (as two divided doses) on days 1–14 (n = 201) of a 21-day cycle (C) in a randomised, open-label, multicentre, phase III trial.[7]

abine combination therapy and capecitabine monotherapy recipients.[19]

- The time since the last dose of trastuzumab (≤8 weeks or >8 weeks) had little effect on the median time to progression for recipients of combination lapatinib plus capecitabine (6.8 and 6.5 months) or capecitabine monotherapy (4.7 and 3.7 months).[19]
- Lapatinib plus capecitabine therapy may reduce the risk of brain metastasis (section 1).[19] In an exploratory analysis, 4 (2%) patients receiving lapatinib plus capecitabine combination therapy and 13 (6%) patients receiving capecitabine monotherapy had brain metastases as the site of first progression ($p = 0.045$).[19]

4. Tolerability

The tolerability of lapatinib in combination with capecitabine was evaluated in the pivotal phase III trial in patients with locally advanced or metastatic, refractory, HER2-positive breast cancer (section 3). This section will focus on the tolerability data from the final analysis of the trial.[7,19]

- Most adverse events were generally mild to moderate in severity.[7,19] The most frequent (i.e. incidence ≥10% in any treatment group) all-grade adverse events occurring in more combination than monotherapy recipients are summarised in figure 2. In addition, fatigue occurred in 24% and 25% of combination therapy and monotherapy recipients.[19]
- Grade 3 or 4 diarrhoea and palmar-plantar erythrodysaesthesia were reported in 14% and 12% of lapatinib plus capecitabine recipients, and 10% and 14% of capecitabine monotherapy recipients.[19] Other adverse events of grade 3 or 4 severity were reported in ≤3% of patients in either treatment group.[19]
- The incidence of laboratory abnormalities was similar in both groups.[7] Grade 3 or 4 haematological (haemoglobin, platelet and neutrophil) or hepatic (AST, ALT and total bilirubin) abnormalities were reported in ≤4% of patients receiving lapatinib plus capecitabine or capecitabine alone.[7]
- Of 198 patients receiving lapatinib plus capecitabine combination therapy, a decrease in LVEF of grade 2 severity was reported in three patients and of grade 3 severity in one patient.[7] More than 60% of all LVEF decreases were reported within the first 9 weeks of therapy.[7]

5. Dosage and Administration

The recommended dosage for lapatinib is 1250mg administered orally once daily on days 1–21 in combination with oral capecitabine 2000 mg/m^2/day given as two divided doses on days

1–14 of a repeating 21-day cycle.[7] It is recommended that lapatinib should be taken 1 hour before or after a meal, whereas capecitabine should be taken with food or within 30 minutes of a meal. Treatment continuation is recommended until disease progression or the occurrence of adverse events. Therapy may be discontinued or interrupted in patients experiencing adverse events of more than grade 2 severity, and discontinued in patients who experience decrease in the LVEF of more than grade 2 severity, which should be monitored throughout therapy. It is also recommended that the concomitant use of CYP3A4 inhibitors or inducers should be avoided and the dose of lapatinib should be reduced in patients with severe hepatic impairment.[7]

For comprehensive dosage and administration guidelines, the local manufacturer's prescribing information should be consulted.

6. Lapatinib: Current Status

Lapatinib has been approved by the FDA for use, in combination with capecitabine, in patients with locally advanced or metastatic HER2-positive breast cancer who have received prior therapy including an anthracycline, a taxane and trastuzumab.[7] Lapatinib plus capecitabine combination therapy is also approved or in preregistration in other European countries[26,27] and Japan.[28]

Median time to progression of disease was significantly longer (by 2 months) with lapatinib plus capecitabine combination therapy than with capecitabine monotherapy in a large, randomised, phase III trial in patients with locally advanced or metastatic, refractory, HER2-positive breast cancer. Adverse events occurring with combination therapy were generally similar in nature to those occurring with capecitabine monotherapy.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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